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PROCEEDINGS

OF THE

CHEMICAL SOCIETY

Minutes of a

SCIENTIFIC MEETING

held in the Zoology Department, King's Buildings, West Mains Road, Edinburgh, on March 30th, 1950, at 11.30 a.m.

The President, SIR IAN HEILBRON, D.S.O., D.Sc., LL.D., F.R.S., was in the Chair.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: David D. Curr, Mowbray Ritchie, Allard H. Johnson, Andrew Davies, R. A. Laidlaw, Wm. Bolton, G. Stein, D. O. Jordan, J. W. Clark-Lewis, G. Crosbie, D. C. Hardwick, I. C. MacWilliam, P. Meares, Angus Marks, William Hay Stafford, Geoffrey M. Gibson, Charles E. Wheelock, W. McCartney, John C. G. M. Holman, F. H. H. Valentin, Alan R. Battersby, J. E. McIntyre, T. R. Bolam, E. G. Peppiatt, E. Lloyd Jones, David M. Wilson, Duncan Taylor, George Fulton, J. A. Eggleston, J. K. Grant, A. M. Smith.

FARADAY LECTURE.

After a brief introduction, the President called upon Professor Dr. G. C. Hevesy, For.Mem.R.S., to deliver the Faraday Lecture entitled, "The Application of Radioactive Indicators in Biochemical Studies."

At the conclusion of the Lecture, a vote of thanks to Professor Hevesy, proposed from the Chair, was carried unanimously, and the President presented the Faraday Medal to the Lecturer.

OFFICIAL ANNOUNCEMENTS

CONGRATULATIONS.

The President has conveyed the congratulations of the Society to the following Fellows, who were elected Fellows of the Royal Society on March 16th, 1950:

Charles Alfred Coulson.
William Joseph Elford.
Ewart Ray Herbert Jones.
Richard Alan Morton.
Maurice Stacey.
Leslie Ernest Sutton.

ANNUAL GENERAL MEETING—1950.

A full report of the One Hundred and Ninth Annual General Meeting held in Edinburgh on March 29th, 1950, will appear in a later issue of the *Journal*.

NOMENCLATURE OF INORGANIC CHEMISTRY.

The Council have approved the decisions of the Publication Committee on nomenclature changes proposed by the Commission for the Nomenclature of Inorganic Chemistry of the International Union of Pure and Applied Chemistry. The names and symbols proposed for various elements are accepted with the exception that the Society does not

propose to change the name of the element tungsten to "wolfram" in any of its publications. The following changes in current practice are involved :—

lutetium in place of lutecium
protactinium in place of protoactinium.

HARRISON MEMORIAL PRIZE.

In accordance with the Trust Deed governing the Harrison Memorial Fund, the Selection Committee, consisting of the Presidents of the Chemical Society, the Royal Institute of Chemistry, the Society of Chemical Industry, and the Pharmaceutical Society, will proceed to make an award of the Harrison Memorial Prize in December 1950, subject to the condition that the Selection Committee shall be of opinion that there is a candidate of sufficient distinction to warrant an award of the Prize.

The Prize, not exceeding £150, will be awarded to the chemist of either sex, being a natural-born British subject and not at the time over thirty years of age, who, in the opinion of the Selection Committee, shall, during the previous five years, have conducted the most meritorious and promising original investigations in Chemistry and published the results of those investigations in a scientific periodical or periodicals.

Applications, five copies of which must be submitted, should give the name of the applicant (in full); age (birth certificate must accompany the application); degrees (with name of University); any other qualifications and experience; titles of published papers (with co-authors names) including full references to publication; where research was carried out; testimonials and references; and any other particulars bearing on the application.

The Selection Committee is prepared to consider applications, nominations, or information as to candidates eligible for the Prize. Any such communication must be received by the President, The Chemical Society, Burlington House, Piccadilly, London, W.1, *not later than Friday, December 1st*, 1950. Candidates must not have attained the age of thirty years at this date.

VAN'T HOFF FUND.

The Committee of the Van't Hoff Fund for the endowment of investigations in the field of pure and applied chemistry invites applications for grants from the fund.

The amount available for 1951 is about 1500 Dutch guilders, and applications should be sent by registered post to "Het Bestuur der Koninklijke Nederlandse Academie voor Wetenschappen, bestemd voor de Commissie van het 'Van't Hoff Fonds,' Trippenhuis, Kloveniersburgwal 29, Amsterdam," before November 1st, 1950. Applicants must state the amount of the grant desired and the purpose for which it is required.

MEETINGS OUTSIDE LONDON.

LIVERPOOL.

"Photo-excited Electron-transfer Reactions," by Professor M. G. Evans, D.Sc., F.R.S.

A meeting was held in the Chemistry Lecture Theatre of the University on March 23rd, 1950, with Professor C. E. H. Bawn in the Chair.

An interesting lecture, illustrated by several simple but well conceived and impressive demonstration experiments, was followed by a vigorous discussion.

A vote of thanks, proposed by Mr. C. A. McDowell, was carried with acclamation.

SHEFFIELD.

"The Treatment of Water for Industrial Purposes," by Mr. P. Hamer.

A joint meeting with the local section of the Royal Institute of Chemistry was held in the Chemistry Lecture Theatre of the University on March 9th, 1950, with Mr. H. C. Hillary, in the Chair.

In an informative review Mr. Hamer dealt with the types of water which come from various sources of supply, and with the problems which arise when these waters are used industrially. He went on to discuss the methods of treatment, and their scientific bases, paying particular attention to the problems of boiler operation.

On the motion of Dr. A. H. Lamberton, a cordial vote of thanks was given to the Lecturer.

" Recent Developments in Acetylene Chemistry," by Professor E. R. H. Jones, D.Sc., F.R.S.

A joint meeting with the University Chemical Society was held in the Chemistry Lecture Theatre of the University on March 16th, 1950, with Professor R. D. Haworth in the Chair.

After a short introduction, Professor Jones dealt with certain important reactions of the $-C\equiv CH$ group—alkylation, carboxylation, and the formation of α-, β-, γ-, and δ-acetylenic alcohols. Partial hydrogenation of acetylenes led to *cis*-addition of the hydrogen atoms, and naturally occurring olefins of *cis*-configuration (*e.g.*, linoleic acid) could be so prepared. Finally, Professor Jones turned to the polyacetylenes of structure $R\cdot[C\equiv C]_n\cdot R$, which may be prepared by oxidative coupling (*e.g.*, $2R\cdot C\equiv CH \longrightarrow R\cdot C\equiv C\cdot C\equiv C\cdot R$), and gave an extremely interesting account of the present position of the research on this topic in progress at Manchester.

On the motion of Dr. J. McKenna, a cordial vote of thanks was given to the Lecturer.

LIST OF APPLICATIONS FOR FELLOWSHIP

(Fellows wishing to lodge objections to the election of these candidates should communicate with the Honorary Secretaries within ten days of the date of publication of the " Journal *" for May 1950. Such objections will be treated as confidential. The forms of applications are available in the Library.)*

***Anet, Edward Felix Lucien John,** M.Sc. (Sydney). British. 79, Tweedmouth Avenue, Rosberry, N.S.W., Australia. Research Student. *Signed by:* R. J. W. Le Fèvre, T. Iredale, S. J. Angyal.

***Bates, Eric Billingsley,** M.Sc. (Manc.). British. 67, Slade Lane, Longsight, Manchester, 13. Research Student at Manchester University. *Signed by:* M. C. Whiting, E. Whittle, H. B. Henbest.

***Baynes-Cope, Arthur David.** British. Trinity College, Dublin. Student. *Signed by:* W. Cocker, K. C. Bailey, C. Lipman.

***Bowles, Denise Elizabeth,** B.Sc. (Lond.). British. 14, Ranelagh Avenue, Barnes, S.W.13. Physical Chemist. *Signed by:* P. J. Killingback, D. C. Hancock, K. Speed.

Derrick, Jack, B.Sc. (Lond.), A.R.I.C., A.M.I.Chem.E. British. Townsend, Randwick, Nr. Stroud, Gloucester. Chemical Engineer. *Signed by:* J. Aldred, A. M. Bremer, E. M. Hunt.

***Fellowes, Kenneth Patrick,** B.Sc. (Lond.). British. Strathdoon, Winterbourne Earls, Nr. Salisbury. Biochemist. *Signed by:* A. F. Childs, L. T. D. Williams, L. R. Hart.

***Goodfellow, Geoffrey Ivor,** B.Sc. (Lond.). British. Downs House, Highways Hostel, Balshaw Lane, Euxton, Lancs. Scientific Officer with Ministry of Supply. *Signed by:* C. J. Riley, P. A. Serin, A. E. Ross.

***Hamilton, Lester Dewie Goodchild,** B.A. (Cantab.). 29, Crowhurst Road, Brixton, S.W. 9. Junior Biochemist. *Signed by:* W. G. Palmer, F. B. Kipping, B. Lythgoe.

***Harper, William Frederick.** British. 23, The Highway, New Inn, Nr. Pontypool. Laboratory Assistant. *Signed by:* R. H. Prince, J. A. Salter, K. W. Miearkis.

Hartley, Albert William Dennis, B.Sc. (Birm.). British. Mooredge Cottage, Old Pool Bank, Pool In Wharfedale, Yorks. Chemist. *Signed by:* R. H. Hopkins, M. Stacey, G. Haynes.

***Hayward, Robin John Richard.** British. 108, Chestnut Grove, New Malden Surrey. Student. *Signed by:* R. H. Hall, E. S. Stern, E. G. E. Hawkins.

Hickman, John Richard, B.Sc. (Lond.), A.R.I.C. British. 22, Lawrie Park Avenue, S.E.26. Works Control Chemist. *Signed by:* J. E. O. Mayne, S. H. A. Hirsch, H. Warson.

Lord, Lawrence Alexander, B.Sc. (Sydney). British. 48, Tambourine Bay Road, Lane Cove, New South Wales, Australia. Technical Representative for The Permutit Co. Ltd., London. *Signed by:* R. J. W. Le Fèvre, L. E. Lyons, T. Iredale.

Miller, Joseph, B.Sc. and Ph.D. (Lond.), A.R.I.C. British. 12, Parkway Nedlands, W. Australia. University Lecturer. *Signed by:* G. A. Ellison, D. E. White, W. Bottomley.

Olivier, Jacques Raymond, B.Sc. Agric. (Reading), A.R.I.C. British. 17, Wardle Avenue, Tilehurst, Reading. Works Chemist at Messrs. Day, Son & Hewitt Ltd., W.1. *Signed by:* S. J. Rowland, H. Bassett, R. L. Collett.

***Owen, Alan John,** B.Sc. (Wales), A.R.I.C. British. 133, Rhyddings Terrace, Brynmill, Swansea. Research Assistant. *Signed by:* C. W. Shoppee, E. E. Ayling, R. H. Davies, D. G. Lewis.

*Phillips, James Ivor, A.R.I.C. British. 39, Mentmore Road, Mosley Hill, Liverpool, 18. Works Analyst. *Signed by:* R. R. Butler, A. E. Findley, L. H. W. Hallett.

Shaw, Thomas Atkinson. British. 39, Agnes Road, Mersey Park, Birkenhead. Research Assistant at the Liverpool Borax Co., Ltd. *Signed by:* W. Murray, J. M. Owen, W. F. Gerrard.

Shine, Henry Joseph, B.Sc. and Ph.D. (Lond.), A.R.I.C. British. Gates & Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California, U.S.A. Research Fellow. *Signed by:* D. B. Smith, J. A. Read, M. C. Berlak.

Staunton, Richard Steedman, B.A. (Oxon.). British. 5, Princes Avenue, West Kirby, Wirral Cheshire. Research Student at Oxford University. *Signed by:* A. S. Bailey, W. A. Waters, K. W. Bentley.

Strawford, Thomas. British. 24, St. Martins Road, Knowle, Bristol, 4. Student at Bristol University. *Signed by:* W. D. Ollis, W. Baker, J. B. Harborne.

*Worthy, Thomas Stanley, B.A. (Cantab.). British. University Chemical Laboratory, Pembroke Street, Cambridge. Research Student. *Signed by:* A. R. Todd, B. C. Saunders, F. G. Mann.

UNDER SPECIAL PROVISIONS APPERTAINING TO CANDIDATES RESIDENT ABROAD.

Benkeser, Robert A., B.S. (Xavier Univ.), M.S. (Detroit), Ph.D. (Iowa State College). American. Chemistry Department, Purdue University, Lafayette, Indiana, U.S.A. Professor. *Signed by:* F. G. Bordwell.

Brewster, James Henry, A.B. (Cornell), Ph.D. (Illinois). American. Chemistry Department, Purdue University, Lafayette, Indiana, U.S.A. Instructor in Chemistry. *Signed by:* F. G. Bordwell.

Brown, Herbert Charles, B.S. and Ph.D. (Chicago). American. Department of Chemistry, Purdue University, Lafayette, Indiana, U.S.A. Professor of Chemistry. *Signed by:* F. G. Bordwell.

Cooper, Glen Dale, B.S. (Arkansas State Coll.), Ph.D. (Purdue). American. Department of Chemistry, Northwestern University, Evanston, Illinois, U.S.A. Research Associate in Chemistry. *Signed by:* F. G. Bordwell.

*Crew, Malcolm Charles, M.A. (Columbia). American. 1040, John Jay Hall, Columbia University, New York 27, U.S.A. Student. *Signed by:* D. Y. Curtin.

Graham, Ronald Powell, M.A. (Queen's), A.M. and Ph.D. (Columbia). Canadian. Department of Chemistry, McMaster University, Hamilton, Ontario, Canada. Associate Professor of Chemistry. *Signed by:* D. C. Lloyd.

Hammond, George Simms, B.S. (Bates Coll.), M.A. and Ph.D. (Harvard). American. Department of Chemistry, Iowa State College, Ames, Iowa, U.S.A. Assistant Professor. *Signed by:* C. A. Bunton.

Kiener, Pierre E., Chem. Eng. (Zürich). Swiss. Apartado 115, Merida, Venezuela. Professor of Chemistry at the University of the Andes. *Signed by:* E. J. Bowen.

Kornblum, Nathan, Ph.D. (Illinois), B.S. (New York). American. Department of Chemistry, Purdue University, Lafayette, Indiana, U.S.A. Associate Professor. *Signed by:* F. G. Bordwell.

Light, Alfred Keith, B.Sc. (Queen's). British. 393, Holland Avenue, Ottawa, Ontario, Canada. Chemist at the National Research Council. *Signed by:* D. C. Lloyd.

Martin, Ewan Cameron, A.R.I.C. Australian. Chemistry Department, Sydney Technical College, Sydney, N.S.W., Australia. Lecturer in Chemistry. *Signed by:* R. L. Collett, H. J. T. Ellingham.

Martin, Lothar, Ph.D. (Zürich). Swiss. Research Institute, 3619, University Street, Montreal, Canada. Research Assistant at the Montreal General Hospital. *Signed by:* C. B. Purves.

Rice, Kenneth James, B.Sc. (McMaster). Canadian. 307 John Street South, Hamilton, Ontario, Canada. Manager of the Westdale New Idea Laundry Ltd., Hamilton. *Signed by:* D. C. Lloyd.

Stevens, William Harmer, M.Sc. (Queen's). Canadian. 16, Wolfe Avenue, Deep River, Ontario, Canada. Assistant Research Chemist at the National Research Council. *Signed by:* F. Brown.

* Reduced annual subscription.

PAPERS RECEIVED.

(List of papers received between March 23rd and April 20th, 1950.)

"Search for new analgesics. Part IV. Variations in the basic side-chain of amidone." By P. Ofner and E. Walton. With a note on some pharmacological results. By A. F. Green and A. C. White.

"New therapeutic agents of the quinoline series. Part VII. 2-, 3-, and 4-Pyridylquinolines, 4-pyridylquinaldines, and 2-pyridyl-lepidines." By D. H. Hey and J. M. Williams.

"The nitration of 4-hydroxy- and 4-chloro-3-methylquinoline." By A. Adams and D. H. Hey.

"The preparation of α-substituted glutaric acids." By M. F. Ansell and D. H. Hey.

" Researches on acetylenic compounds. Part XXIV. Diels–Alder reactions with acetylenic keto-esters." By T. Y. Shen and M. C. Whiting.

" The separation of mixtures of solutes by distribution between solvents. Part III. The separation of solutes by discontinuous distribution between solvents." By John D. A. Johnson.

" The chemistry of reductone. Part II. Some condensation products of reductone with amino-compounds." By Wesley Cocker, R. A. Q. O'Meara, J. C. P. Schwarz, and E. R. Stuart.

" Polymorphism in tetraethyl-tin and -lead." By L. A. K. Staveley, H. P. Paget, B. B. Goalby, and J. B. Warren.

" Amino-acid complexing in lanthanon separation." By R. C. Vickery.

" Note on the double salts, sodium cobalt sulphate and sodium magnesium sulphate." By Henry Bassett and (the late) Joseph H. Henshall.

" The chemistry of hop constituents. Part I. Humulinone, a new constituent of hops." By A. H. Cook and G. Harris.

" Syntheses in the penicillin field. Part IX. A new synthesis of penicillamine, and attempts to obtain new types of penicillins." By A. H. Cook, G. Harris, J. R. A. Pollock, and J. M. Swan.

" Studies in the azole series. Part XXIX. The preparation of some natural xanthines and related purines." By A. H. Cook and G. H. Thomas.

" Studies in the azole series. Part XXX. New syntheses of 2- and 8-aminopurines." By A. H. Cook and G. H. Thomas.

" Studies in the azole series. Part XXXI. The interaction of amines and 2-mercapto-4-alkylidene- or -arylidene-thiazolin-5-ones." By A. H. Cook, G. D. Hunter, and J. R. A. Pollock.

" Studies in the azole series. Part XXXII. Syntheses of peptides of substituted cysteines." By A. H. Cook and J. R. A. Pollock.

" The synthetic application of phenylarsinebis(magnesium bromide). Part I. The synthesis of *iso*arsindolines, tetrahydro*iso*arsinolines, and 2-arsaperinaphthanes." By M. H. Beeby, Gerald H. Cookson, and Frederick G. Mann.

" The synthetic application of phenylarsinebis(magnesium bromide). Part II. The synthesis and properties of 6-substituted 6-arsa-1 : 2-3 : 4-dibenz*cyclo*hepta-1 : 3-dienes." By M. H. Beeby, F. G. Mann, and E. E. Turner.

" Purpurogallin. Part III. Synthesis of purpurogallin and some analogues." By David Caunt, Wilfrid D. Crow, Robert D. Haworth, and Charles A. Vodoz.

" First-order asymmetric transformation arising from solvation." By J. Glazer, Margaret M. Harris, and E. E. Turner.

" Organoalkalimetallic compounds. Part I. The reaction of benzylsodium with alkyl halides." By D. Bryce-Smith and E. E. Turner.

" Mechanism of the benzidine rearrangement." By E. D. Hughes and C. K. Ingold.

" Quantitative analysis of mixtures of sugars by the method of partition chromatography. Part V. Improved methods for the separation and detection of the sugars and their methylated derivatives on the paper chromatogram." By L. Hough, J. K. N. Jones, and W. H. Wadman.

" The synthesis of 2- and 6-amino-3-hydroxybenzenesulphonamides." By D. V. Parke and R. T. Williams.

" Derivatives of benz-1 : 2 : 4-thiadiazine 1 : 1-dioxide." By D. V. Parke and R. T. Williams.

" Complexes of copper phenylacetate and diphenylacetate with alcohols." By Malcolm Crawford.

" A new route to the phthalide-*iso*quinoline bases, and a synthesis of (—)-hydrastine." By Robert D. Haworth and A. Reginald Pinder.

" Properties and reactions of free alkyl radicals in solution. Part I. Some reactions of the 2-cyano- and the 2-carbomethoxy-2-propyl radicals with quinones." By A. F. Bickel and W. A. Waters.

"Reaction-kinetic investigations of the incomplete dissociation of salts. Part II. The hydrolysis of carbethoxymethyltriethylammonium iodide and of ethyl acetate by solutions of metallic hydroxides." By R. P. Bell and (Mrs.) G. M. Waind.

"The pigments of 'dragon's blood' resins. Part I. Dracorubin." By (Mrs.) Dorothy A. Collins (née Jones), Fred Haworth, Kalya Isarasena, and Alexander Robertson.

"The pigments of 'dragon's blood' resins. Part II. A synthesis of dracorhodin." By Alexander Robertson and W. B. Whalley.

"Electrolyte absorption by alginate gels without and with cation exchange." By I. L. Mongar and A. Wassermann.

"The intrinsic viscosity of sodium alginate." By M. L. R. Harkness and A. Wassermann.

"Ion exchange and swelling of alginate gels." By I. L. Mongar and A. Wassermann.

"Influence of ion exchange on elastic properties of fully swollen alginate fibres." By I. L. Mongar and A. Wassermann.

"Ion exchange and molecular shape of alginate chains; birefringence measurements." By I. L. Mongar and A. Wassermann.

"Heat effects accompanying the adsorption of simple electrolytes by fully swollen alginate and cellulose gels. A new micro-colorimetric method." By I. L. Mongar and A. Wassermann.

"Ion exchange and fibre contraction." By I. L. Mongar and A. Wassermann.

"Residual currents." By Edgar Newbery

"The structure of a cell-wall polysaccharide of baker's yeast." By D. J. Bell and D. H. Northcote.

"Peroxides of tetrahydrocarbazole and related compounds. Part I. Tetrahydrocarbazole peroxide." By R. J. S. Beer, L. McGrath, and Alexander Robertson.

"Derivatives of thiophen of biological interest. Part I. Thiophen analogues of stilbene and of related compounds." By Ng.Ph. Buu-Hoi, Ng. Hoan, and Denise Lavit.

"Characterisation of 3 : 4-dimethyl D-glucose." By D. J. Bell and G. D. Greville.

"The reaction of phenols with phenyl and α-naphthyl *iso*cyanate." By J. M. Lyons and R. H. Thomson.

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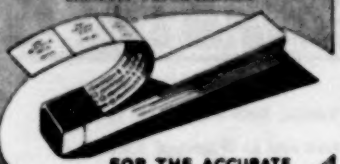

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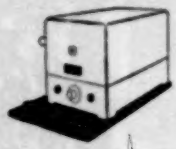

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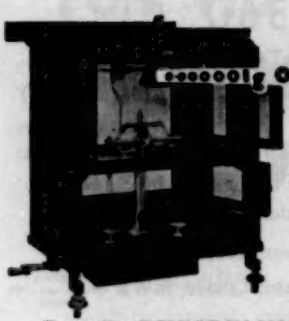

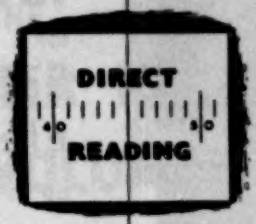

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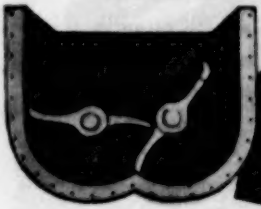

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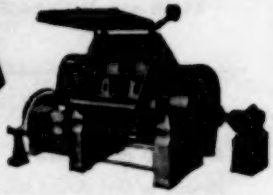

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OBITUARY NOTICE.

ARNOLD STEVENSON, M.B.E.

1874—1948.

Arnold Stevenson was born in London on the 9th July 1874 and was the son of the well-known architect J. J. Stevenson, F.R.I.B.A.; his mother, née Jane Omond, came of an Orkney family. After attending a preparatory school near his home in Bayswater Stevenson went to Winchester in 1888. While there he did well in Mathematics, and then became greatly interested in Natural Science, particularly in Chemistry. He was also a very keen member of the Rifle Corps, in which he held the rank of Colour Sergeant, the highest attained by anyone who was not a master. He represented Winchester in the competition for the Ashburton Shield at Bisley.

In 1893 Stevenson won a Minor Scholarship to Clare College, Cambridge, and in 1894 a Foundation Scholarship. He lost a year through illness and took the Natural Sciences Tripos, Part I, in 1897, and Part II the following year. After studying for a year in Aachen he joined the Z Lamp Co. who manufactured incandescent lamps near Wimbledon.

Soon after the outbreak of the first World War Stevenson offered his services to Professor (later Sir Jocelyn) Thorpe who at that time led a team of pupils at the Imperial College of Science and Technology, engaged in the manufacture of drugs for the use of the Services. Here Stevenson was associated with Miss H. M. Judd and the writer, who found the meticulously painstaking newcomer a great help.

When the Ministry of Munitions was founded Stevenson went to the Optical Glass Section; he was given the M.B.E. for his services there in 1918. In the following year he decided to do research in Organic Chemistry and joined Thorpe's school at South Kensington, where he stayed for some years. Here again his love of order and method proved valuable. He published a number of papers in collaboration with Thorpe and Kon, and then worked with a junior collaborator. His papers dealt mainly with the formation of tetrahydronaphthalene derivatives (with Kon, *J.*, 1921, 87; with Thorpe, *J.*, 1922, 1717; with Attwood and Thorpe, *J.*, 1923, 1755). Following up this work he made the interesting observation that an oxidation product of a tetrahydronaphthalene derivative exhibited a novel form of tautomerism, for which the term ring-chain tautomerism was coined (with Kon and Thorpe, *J.*, 1922, 650). In the search for other examples of such tautomerism Stevenson re-examined an oxidation product of camphor known as Balbiano's acid (*loc. cit.*) the preparation of which was a particularly arduous piece of work. This, and the lengthy preparation of suberone (with Day and Kon, *J.*, 1920, 639), he undertook cheerfully.

In the early 1920's Thorpe's research school was growing rapidly and there arose problems in the supply of research chemicals for the numerous students. Stevenson became interested in this and for a number of years ran a "shop" where ethyl malonate, ethyl cyanoacetate, and many other chemicals, procured in bulk, were sold to students without profit. To this task he devoted himself with enthusiasm and meticulous care, and many generations of research students will remember the somewhat stooping, grey figure of "Steve," as he was affectionately nicknamed, carefully doling out research materials.

Personally, Stevenson was of a shy and retiring disposition. An old bachelor, he spent much of his leisure at the Savile Club and had a vast store of memories about the academic world, particularly that centred about his old University. He took a great interest in the careers of his friends although he himself was not ambitious and might well have achieved more had he so chosen. With his passing we mourn a courteous gentleman of an old and vanishing kind, and a very loyal friend.

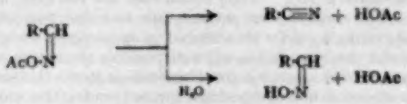
G. A. R. Kon.

249. *The Isomerism of the Oximes. Part XXXIX. The Hydrolysis of Acyl Derivatives.*

By M. Benger and O. L. Brady.

The mechanism of the alkaline hydrolysis of acyl derivatives of substituted benzaldoximes has been studied and it has been shown that the main reactions are attack by hydroxyl ions (1) at the methine-hydrogen atom, resulting in the formation of the nitrile, and (2) at the carbonyl-carbon atom, resulting in the formation of the oxime. The effects of different substituents in the nucleus and of varying the acyl group have been investigated and many of the apparently anomalous results obtained in the hydrolysis of acyl-aldoximes have been explained.

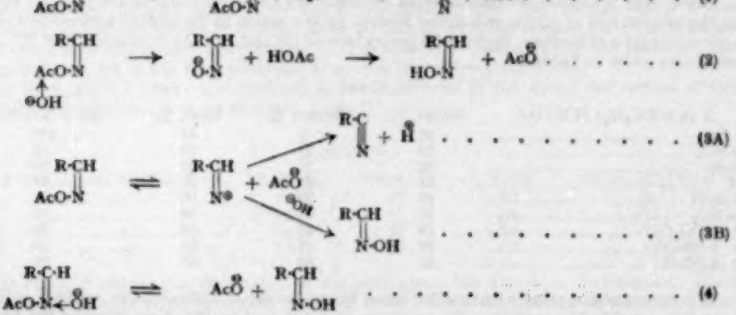
When the acetyl derivative of an aromatic β-aldoxime is warmed in the solid state with 2N-sodium carbonate, or when its solution in acetic anhydride is shaken with a large excess of the same reagent, the main reaction is the elimination of acetic acid and the formation of nitrile, but some β-aldoxime is also formed :



Certain exceptions to this reaction are mentioned below.

When the sodium carbonate is replaced by 2N-sodium hydroxide the amount of nitrile formed is smaller and that of β-aldoxime larger (Hantzsch, *Ber.*, 1891, **24**, 38; *Z. physikal. Chem.*, 1894, **13**, 509; Brady and McHugh, *J.*, 1925, **127**, 2423; Hauser and Sullivan, *J. Amer. Chem. Soc.*, 1933, **55**, 4611; Hauser and Jordan, *ibid.*, 1935, **57**, 2450).

The decomposition of an acetyl-β-aldoxime in the presence of alkali can be represented as taking place in four ways :



Mechanism (1) consists in the removal of a proton from the methine group by a hydroxyl ion, and gives the nitrile as the sole product. Mechanism (2) consists in attack by a hydroxyl ion at the carbonyl group and corresponds to acyl–oxygen fission in the alkaline hydrolysis of esters (Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686). This will yield oxime only. Mechanism (3) represents ionisation of the acetyl derivative or, in other words, escape of the acetoxyl group with the pair of electrons binding it to nitrogen, corresponding to the unimolecular alkyl–oxygen fission in the alkaline hydrolysis of esters, for which evidence is supplied by the work of Kenyon and his collaborators (Kenyon, Partridge, and Phillips, *J.*, 1936, 85; Hills, Kenyon, and Phillips, *ibid.*, p. 582; Kenyon, Partridge, and Phillips, *J.*, 1937, 216). The cation produced may behave in two ways : extrusion of the methine-hydrogen as a proton may occur

with the formation of nitrile (3A), or attack by a hydroxyl ion with the formation of oxime (3B). In the case of the decomposition of acyl-β-aldoximes it is unlikely that oxime formation occurs to any considerable extent by this mechanism, as the addition of hydroxyl to the cation would give the more stable α-aldoxime, whereas, in practice, the oxime formed consists of the nearly pure β-isomeride (Brady and McHugh, Sullivan, and Hauser, *loc. cit.*). The nitrogen cation may be more stable than an alkyl cation, so the speed of mechanism (3A) relative to (2) may be greater than in the case of esters, and consequently ionisation may play a greater part in the hydrolysis of acyl-β-aldoximes than in the case of esters.

As pointed out by Day and Ingold (*loc. cit.*), referring to esters, if the hydroxyl ion is replaced by successive weaker nucleophilic reagents, both acyl and alkyl attack will be reduced in speed and may ultimately become slower than the rate of ionisation, which suggests that the increase in the proportion of nitrile formed when 2N-sodium carbonate is employed may be due to its formation to a greater extent by mechanism (3A).

Hantzsch (*Z. physikal. Chem.*, 1894, **13**, 509) and Ley (*ibid.*, 1895, **18**, 376) measured the velocity of acid formation when various acetyl-β-aldoximes (M/100) in aqueous alcohol were decomposed by sodium acetate (M/100). They found that the reaction, under these conditions, was of the first order; their results thus do not rule out the possibility of the first-order mechanism (3A), but they cannot safely be adduced in its support owing to the ambiguity of the reaction mechanism and the complications from possible stereoisomeric change during the experiments, which would be favoured by the liberated proton. Unfortunately no evidence is produced about the nature of the compounds formed under the experimental conditions of the velocity measurements, it being assumed that nitrile and acetic acid were the only products. Hantzsch also investigated the reaction between acetyl-β-benzaldoxime and sodium carbonate, both in M/200-solution, but obtained inconstant values for a second-order reaction about 100 times faster than the previous one. He does not seem to have considered the possibility of a first-order reaction in this case, and does not give full experimental values.

The last-mentioned mechanism (4), *i.e.*, attack by hydroxyl at the nitrogen with the extrusion of the acetoxyl ion leading to oxime, a replacement reaction, is ruled out, as it would involve stereoisomeric change with the production of the α-aldoxime.

Oxime formation in the presence of 2N-sodium hydroxide is therefore due essentially to mechanism (2); it remains to be considered whether mechanism (1) or (3A) is principally concerned in nitrile formation in the alkaline decomposition of acetyl-β-aldoximes.

Some light is thrown on this question by the effect of substituents in the benzene nucleus on the proportions of nitrile and oxime formed by the action of 2N-sodium hydroxide at 0° on various acetyl-β-aldoximes, that is the proportion of (1) and/or (3A) compared with (2). The results are given in Table I.

TABLE I.

X in β-X·C_6H_4·CH:N·OAc.	Nitrile, %.	Oxime, %.	Total, %.	Nitrile, % of total.
o-NO_2	85	0	85	100
p-NO_2	75	21	96	78
p-Me	61	27	88	70
H	61	30	91	67
p-MeO	66	33	99	66
m-NO_2	57	31	88	65
3 : 4-CH_2O_2	48	48	96	50
3 : 4-$(MeO)_2$	36	55	91	40
2 : 4-$(MeO)_2$	31	64	95	32

We do not claim great accuracy for these figures owing to difficulties in working with the unstable acetyl-β-aldoximes, but the positions of the *o*- and *p*-nitro-derivatives at the head of the Table and of the 3 : 4-methylenedioxy- and 3 : 4- and 2 : 4-dimethoxy-derivatives at the bottom is sufficiently significant to establish the influence of the electronic properties of the substituent in the benzene nucleus on the proportion of nitrile to oxime formed. The results are probably not accurate enough to fix the relative positions of the compounds in which X is *p*-Me, H, *p*-OMe, or *m*-NO_2. Hauser and his co-workers (*loc. cit.*) have investigated the same reaction in the case of four acetyl β-aldoximes; they obtained a much smaller proportion of nitrile, but their order was *p*-nitro > *m*-nitro > 3 : 4-methylenedioxy > *p*-methoxy.

Now the negative inductive effect of the nitro-group will facilitate attack by hydroxyl ions at the methine-carbon atom, favouring mechanism (1), and will also facilitate attack by hydroxyl ions at the carbonyl group, the latter less effectively owing to its remoteness from

the activating group. The inductive effect will hinder the ionisation demanded by mechanism (3A).

The negative mesomeric and electromeric effects of the nitro-group would facilitate the attack at the methine-hydrogen atom, and if the conjugation extends effectively to the oxygen atom would facilitate attack at the carbonyl group owing to the inductive effect of the positive oxygen atom.*

Since the effect of the nitro-group is always to hinder the ionisation mechanism (3A), the greater yield of nitrile from acetyl-β-*p*-nitrobenzaldoxime than from acetyl-β-benzaldoxime indicates that in this case mechanism (3A) plays a small part in the reaction and that mechanism (1) is the controlling factor.

The influence of methoxyl groups is more difficult to interpret. The negative inductive effect would be the same as with the nitro-group—to facilitate mechanisms (1) and (2) and to hinder mechanism (3A). The smaller proportion of nitrile to oxime obtained in the decomposition of, for example, acetyl-β-2 : 4-dimethoxybenzaldoxime compared with acetyl-β-benzaldoxime suggests again that mechanism 3A is less important in nitrile formation than is mechanism (1).

The action of sodium hydroxide on the propionyl derivatives of some β-aldoximes has also been investigated. The results obtained when the solid propionyl-β-aldoxime was treated with 2N-sodium hydroxide are shown in Table II, and those for a solution of the propionyl-β-aldoxime in propionic anhydride shaken with a large excess of 2N-sodium hydroxide are shown in Table III. The latter method was employed because it was found impossible to isolate the propionyl derivatives sufficiently pure.

TABLE II.

X in β-X·C_6H_4·CH:N·O·COEt.	Nitrile, %.	Oxime, %.	Total.	Nitrile, % of total.
p-NO_2	63	36	99	63
3 : 4-CH_2O_2	41	57	98	42

TABLE III.

X in β-X·C_6H_4·CH:N·O·COEt.	Nitrile, %.	Oxime, %.	Total.	Nitrile, % of total.
p-Cl	77	22	99	78
p-Me	73	21	94	78
p-MeO	65	32	97	67

The propionyl derivatives are less easily decomposed than the corresponding acetyl compounds, and it was necessary to leave them in contact with the reagent for a much longer period, thus affording greater opportunity of stereoisomeric change during the reaction; the results, however, are in the same order as those from the acetyl-β-aldoximes.

The same general effects are observed in the hydrolysis of the acetyl derivatives of the substituted cinnamaldoximes, as shown in Table IV.

TABLE IV.

X in β-X·C_6H_4·CH:CH·CH:N·OAc.	Nitrile, %.	Oxime, %.	Total.	Nitrile, % of total.
m-NO_2	78	17	95	82
H	69	27	96	72
p-MeO	54	38	92	59
o-MeO	48	49	97	49

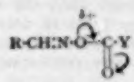
The effect of changes in the nature of the acyl group has also been investigated; since suitable acyl derivatives could not be prepared from β-aldoximes those of α-aldoximes have been used, but it was necessary in some cases to carry out the hydrolysis at a higher temperature owing to the greater stability of acyl-α-aldoximes.

It was found that propionyl- and *n*-heptoyl-α-aldoximes, on hydrolysis at 100° with 2N-sodium hydroxide, gave only the α-aldoximes, and a similar result was obtained with mono-

* From a kinetic study of the alkaline hydrolysis of the acetyl derivatives of nuclear-substituted acetophenone oximes, in which there is no methine-hydrogen atom open to attack, it has been found that varying a *para*-substituent has very little influence on the rate constant of the hydrolysis; indeed the effect seems to be in the opposite sense to that here suggested; *e.g.*, *p*-NO_2·C_6H_4·CMe:N·OAc is hydrolysed about 6% slower than *p*-MeO·C_6H_4·CMe:N·OAc. The kinetics, however, are complicated owing to the varying acid strengths of the oximes produced in the reaction which compete differentially for $\bar{O}H$ ions (Brady and Miller, unpublished).

chloroacetyl derivatives, but trichloroacetyl-α-*p*-nitro- and trichloroacetyl-α-3 : 4-methylenedioxy-benzaldoximes with 2N-sodium hydroxide at 0° gave 35% and 10% of nitrile, respectively, whilst *o*-nitrobenzoyl-α-*p*-nitrobenzaldoxime gave at 100° 50% of nitrile. Hauser, Jordan, and O'Connor (*J. Amer. Chem. Soc.*, 1935, **57**, 2456) have also reported the formation of nitrile, or the corresponding carboxylic acid formed by its hydrolysis, in the decomposition of carbethoxy-α-aldoximes by 2N-sodium hydroxide at 97—100°, obtaining from the carbethoxy-derivatives of α-*m*-nitro- 50%, α-*p*-nitro- 48%, α-*p*-chloro- 53%, α-*p*-methoxy- 31%, and α-3 : 4-methylenedioxy-benzaldoxime 34% of nitrile or acid.

In considering these results, one must bear in mind that normally (an exceptional case is dealt with below) neither β-aldoximes nor α-aldoximes with alkalis give any of the nitrile. In alkaline solution the oximes will exist mainly as anions $R\cdot CH{:}N\cdot O^{\ominus}$ and the high electron density in the neighbourhood of the oxygen atom prevents attack by hydroxyl ions at the methine-hydrogen atom; when the hydrogen of the hydroxyl group is replaced by an acyl group the mesomeric effect, by establishing a positive pole at the oximino-oxygen atom, reduces the electron concentration sufficiently to allow attack at the methine-hydrogen atom provided (*a*) that there are suitable substituents in the benzene nucleus R, and (*b*) that the stereo-chemical structure is favourable:

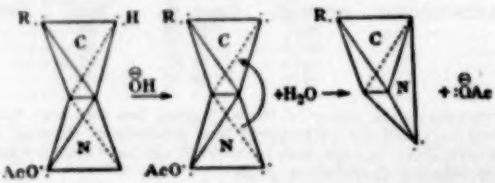


Varying Y will either oppose or reinforce this effect. If Y is electron-repelling it will compete with the oximino-oxygen atom in supplying electrons to the carbonyl oxygen atom, and if electron-attracting it will have the opposite effect.

Where Y is an alkyl group its competition is sufficient to prevent nitrile formation from the acyl-α-aldoxime where the stereochemical structure is unfavourable to the removal of the methine hydrogen, but not enough to prevent it where the stereochemical structure is not unfavourable and the substituent in the benzene nucleus is favourable, that is, in the acyl-β-aldoximes. Where Y is CCl_3 the strong inductive effect will cause a greater demand on the electrons of the oximino-oxygen atom, and the trichloroacetyl derivatives of α-aldoximes yield some nitrile.

Where Y induces sufficient electron-withdrawal, mechanism 3A will come into play (see Ambrose and Brady, *J.*, 1950, 1243), but it cannot be the sole mechanism of nitrile formation in alkaline hydrolysis, since trichloroacetyl-α-*p*-nitrobenzaldoxime gives more nitrile than does trichloroacetyl-α-3 : 4-methylenedioxybenzaldoxime.

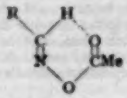
Mention has been made above that there is a favourable stereochemical configuration for attack at the methine-hydrogen atom by hydroxyl ions, and some explanation is necessary. Mills (*British Ass. Rept.*, 1932, 47) first suggested that nitrile formation consisted in removal of a proton from the methine group, accompanied by a movement of the nitrogen towards the carbon atom, with the ultimate extrusion of the acetate ion (see figure).



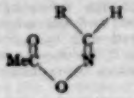
This mechanism was held to explain the fact that the elimination of acetic acid with the formation of nitrile occurred more readily when the methine-hydrogen atom and the acetyl group were on opposite sides of the plane of the carbon–nitrogen double bond, since then the acetyl group would not interfere with the movement of the nitrogen towards the carbon atom.

We think, however, that the greater reluctance of the α- compared with the β-isomeride to yield nitrile is due chiefly to greater difficulty of attack by the hydroxyl ion on the methine-hydrogen atom, owing to the influence of the unshared electrons of the carbonyl-oxygen atom on the methine-hydrogen atom leading perhaps to hydrogen bonding; this can occur in the α-,

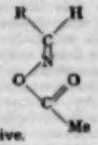
but is less likely in the β-isomeride (for further discussion of this see Ambrose and Brady, *loc. cit.*).



α-Acetyl derivative.

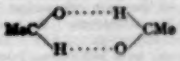


or



β-Acetyl derivative.

Evidence of hydrogen bonding involving a methine-hydrogen atom appears from the infra-red absorption spectrum of acetaldehyde which has been represented :



(Alexander and Lambert, *Trans. Faraday Soc.*, 1941, **37**, 421).

The considerations here advanced clear up a number of anomalies in the behaviour of acyl derivatives of the aldoximes.

The di- and tri-nitrophenyl derivatives of the aldoximes (Brady and Truszkowski, *J.*, 1924, **125**, 1087; Brady and Klein, *J.*, 1925, **127**, 844), when boiled with 2N-sodium hydroxide, give exclusively nitriles or their hydrolysis products, the acids, and the β-structure has been assigned to them despite the fact that they were formed from α-aldoximes and not from β-aldoximes. The strong electron-withdrawal due to the di- and tri-nitrophenyl groups would, however, greatly favour nitrile formation by mechanisms 1 and 3A and, in addition, there is no carbonyl group to stabilise the methine-hydrogen atom in the α-isomeride. In consequence there is no reason why these compounds should not be given the α-configuration.

The diphenylcarbamyl derivatives prepared by the action of diphenylcarbamoyl chloride on the sodium salts of the α-aldoximes give, on alkaline hydrolysis, nitriles almost exclusively (Brady and Dunn, *J.*, 1913, **103**, 1613); on the other hand the carbamyl- (Conduché, *Ann. Chim. Phys.*, 1908, [viii], **13**, 5), phenylcarbamyl-, naphthylcarbamyl-, phenylethylcarbamyl-, and diethylcarbamyl-α-aldoximes give on alkaline hydrolysis mainly the oximes (Brady and Dunn, *J.*, 1916, **109**, 650; Brady and Ridge, *J.*, 1923, **123**, 2163; Brady and McHugh, *J.*, 1925, **127**, 2414).

These results are explicable when one considers the electron density at the carbamyl nitrogen atom in the light of the strength, as bases, of diphenylamine, ammonia, aniline, naphthylamine, ethylaniline, and diethylamine. Only when two phenyl groups are present is the electron-withdrawal sufficient to cause nitrile formation, and there is little doubt that the diphenylcarbamyl derivatives have the α-configuration.

Two other earlier difficulties may now be considered. Certain acetyl derivatives of β-aldoximes do not give nitrile on treatment with 2N-sodium carbonate, for example, those of β-5-bromo-3 : 4-dimethoxybenzaldoxime (Brady and Wentworth, *J.*, 1920, **117**, 1045), β-3 : 4-dimethoxybenzaldoxime (Brady and Dunn, *J.*, 1923, **123**, 1783), and β-2 : 4-dimethoxybenzaldoxime (see Experimental section), though they are decomposed by 2N-sodium hydroxide. Here the mesomeric effect is sufficient to prevent attack at the methine-hydrogen atom when the hydroxyl-ion concentration is low.

The aldoximes themselves are not normally converted into nitriles by the action of hydroxyl ions on the methine-hydrogen atom, but α-*o*-nitrobenzaldoxime on heating with aqueous sodium hydroxide readily gives the nitrile (Reissert, *Ber.*, 1908, **41**, 3815; Brady and Goldstein, *J.*, 1926, 1918). The effect of the nitro-group in the *ortho*-position is sufficiently strong to enable a proton to be removed from the methine group without the additional help provided by the carbonyl group of the acyl group.

Experimental.

Preparation of Materials.

Most of the compounds used have been previously described.

β-Oximes.—*β-2 : 4-Dimethoxybenzaldoxime* was prepared by dissolving 2 : 4-dimethoxybenzaldoxime (5 g.) (previously dried over phosphoric oxide) in dry benzene (100 c.c.) at 60°, passing in a rapid stream of dry hydrogen chloride for 15 seconds, and scratching the sides of the vessel. The β-hydrochloride, m. p. 153° (decomp.), was collected and decomposed with 2N-sodium carbonate (large excess), and the precipitated oxime collected and crystallised from benzene in long needles, m. p. 135° (Found : C, 59·9;

H, 6·0. $C_9H_{11}O_3N$ requires C, 59·7; H, 6·1%). Even with these precautions the preparation failed several times, the hydrochloride giving the α-oxime.

The method of Brady and Dunn (*J.*, 1923, **123**, 1783) for the preparation of *β*-3 : 4-dimethoxybenzaldoxime was not satisfactory and the following proved much better. α-3 : 4-Dimethoxybenzaldoxime was dissolved in dry ether, and the α-hydrochloride precipitated with dry hydrogen chloride. This was collected, just covered with concentrated hydrochloric acid, and heated on the steam-bath for a few minutes, whereupon it dissolved; the solution was poured into a large excess of well stirred 2*N*-sodium carbonate, an emulsion being formed which soon deposited colourless crystals of *β*-3 : 4-dimethoxybenzaldoxime.

Attempts by various methods to prepare *β*-o-methoxy-, *β*-o-ethoxy-, *β*-2 : 5-dimethoxy-, and *β*-2 : 4 : 6-trimethoxy-benzaldoxime were unsuccessful.

Acetyl-α-aldoximes.—Prepared by the usual method, *acetyl-α-2 : 4-dimethoxybenzaldoxime* crystallised from benzene–light petroleum in needles, m. p. 89° (Found: C, 58·8; H, 5·9. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·8%), and *acetyl-α-2 : 5-dimethoxybenzaldoxime* from the same solvent in needles, m. p. 58° (Found: C, 59·3; H, 5·9%).

Propionyl-α-aldoximes.—The α-aldoxime (5 g.) was dissolved in propionic anhydride (7 c.c.) with slight warming, and the solution cooled in ice–salt, whereupon the propionyl derivative crystallised. It was recrystallised from benzene–light petroleum. Prepared in this way, *propionyl-α-p-nitrobenzaldoxime* crystallised in pale yellow needles, m. p. 112° (Found: C, 54·0; H, 4·3. $C_{10}H_{10}O_4N_2$ requires C, 54·0; H, 4·5%), *propionyl-α-m-* as a colourless powder, m. p. 74° (Found: C, 54·1; H, 4·4%), and *propionyl-α-o-nitrobenzaldoxime* as plates, m. p. 62° (Found: C, 54·2; H, 4·7%), and *propionyl-α-3 : 4-methylenedioxybenzaldoxime* as prisms, m. p. 95° (Found: C, 59·6; H, 5·0. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0%). When, instead of cooling the solution in propionic anhydride it was shaken with an excess of 2*N*-sodium carbonate and the precipitated solid was recrystallised, *propionyl-α-o-methoxybenzaldoxime* was obtained from benzene–light petroleum as plates, m. p. 45° (Found: C, 63·5; H, 6·0. $C_{11}H_{13}O_3N$ requires C, 63·7; H, 6·3%), *propionyl-α-3 : 4-dimethoxybenzaldoxime* from carbon tetrachloride and light petroleum as prisms, m. p. 66° (Found: C, 60·7; H, 6·2. $C_{12}H_{15}O_4N$ requires C, 60·7; H, 6·3%), and *propionyl-α-p-chlorobenzaldoxime* from light petroleum as plates, m. p. 71° (Found: C, 56·6; H, 4·7. $C_{10}H_{10}O_2NCl$ requires C, 56·7; H, 4·7%). Propionyl-α-*p*-methoxybenzaldoxime did not solidify in the sodium carbonate but was extracted with ether; the solvent was removed and the oil covered with light petroleum and scratched, a white powder being obtained, having m. p. 45° (Found: C, 63·9; H, 6·7. $C_{11}H_{13}O_3N$ requires C, 63·7; H, 6·3%).

Monochloroacetyl-α-aldoximes.—The α-aldoxime (5 g.) was dissolved in monochloroacetic anhydride (6·5 g.), heated just above its m. p. (45°), and the solution shaken with excess of 2*N*-sodium carbonate. The product was collected and crystallised from benzene–light petroleum, giving *monochloroacetyl-α-p-nitrobenzaldoxime* as greenish-white plates, m. p. 131° (Found: C, 44·5; H, 2·8. $C_9H_7O_4N_2Cl$ requires C, 44·5; H, 2·9%), *monochloroacetyl-α-m-nitrobenzaldoxime* as greenish-white needles, m. p. 129° (Found: C, 44·5; H, 2·9%), *monochloroacetyl-α-o-nitrobenzaldoxime* as plates, m. p. 94° (Found: C, 44·6; H, 3·1%), *monochloroacetyl-α-benzaldoxime* from light petroleum as silky needles, m. p. 84° (Found: C, 54·9; H, 4·2. $C_9H_8O_2NCl$ requires C, 54·7; H, 4·1%), *monochloroacetyl-α-p-methoxybenzaldoxime* from light petroleum as plates, m. p. 60° (Found: C, 53·0; H, 4·3. $C_{10}H_{10}O_3NCl$ requires C, 52·8; H, 4·4%), and *monochloroacetyl-α-3 : 4-dimethoxybenzaldoxime* from light petroleum–carbon tetrachloride as needles, m. p. 101° (Found: C, 51·4; H, 4·7. $C_{11}H_{12}O_4NCl$ requires C, 51·3; H, 4·7%).

Trichloroacetyl-α-aldoximes.—*α-p*-Nitrobenzaldoxime (2 g.) was dissolved at 30° in trichloroacetic anhydride (7 g.), poured into excess of 2*N*-sodium carbonate, and shaken till solid had separated. This was collected at once, dried on porous tile, and crystallised from benzene–light petroleum. *Trichloroacetyl-α-p-nitrobenzaldoxime* crystallised in prisms, m. p. 130°. The trichloroacetyl derivatives are very unstable and cannot be kept for more than a few hours, so for analytical purposes the trichloroacetyl group was at once determined by dissolving the compound in a known excess of 0·2*N*-sodium hydroxide and back-titrating with 0·2*N*-hydrochloric acid (methyl-orange) (Found: $C_9HO_3Cl_3$, 52·0. $C_9H_4O_4N_2Cl_3$ requires $C_9HO_3Cl_3$, 52·5%).

In the case of α-*m*-nitrobenzaldoxime the solution in the warm anhydride was decomposed with water, and the precipitate crystallised from light petroleum as colourless needles, m. p. 93—94° (Found: $C_9HO_3Cl_3$, 50·7%).

In the remaining cases the oxime was dissolved in the anhydride at 0° and poured into ice-cold water. *Trichloroacetyl-α-3 : 4-methylenedioxybenzaldoxime* crystallises from carbon tetrachloride in needles, m. p. 93° (Found: $C_9HO_3Cl_3$, 53·2. $C_{10}H_6O_4NCl_3$ requires $C_9HO_3Cl_3$, 52·6%), and *trichloroacetyl-α-3 : 4-dimethoxybenzaldoxime* from carbon tetrachloride–light petroleum as plates, m. p. 92° (Found: $C_9HO_3Cl_3$, 50·9. $C_{11}H_{10}O_4NCl_3$ requires $C_9HO_3Cl_3$, 50·1%). In spite of every precaution the addition of α-benzaldoxime and α-*p*-methoxybenzaldoxime to trichloroacetic anhydride produced a violent reaction and brown oils smelling strongly of the respective nitriles were obtained.

n-Heptoyl-α-aldoximes.—The α-aldoxime (5 g.) was heated on a water-bath for 15 minutes with *n*-heptoic anhydride (8 c.c.) and cooled. After 24 hours *n-heptoyl-α-p-nitrobenzaldoxime* crystallised, and after recrystallisation from light petroleum formed pale green soapy plates, m. p. 60° (Found: C, 60·0; H, 6·0. $C_{14}H_{18}O_4N_2$ requires C, 60·4; H, 6·5%). *n*-Heptoyl-α-*m*-nitrobenzaldoxime was precipitated by stirring the solution in the anhydride with 2*N*-sodium carbonate, and extracting the product with ether and washing it with light petroleum; the product is an oil which on cooling gave a pale green crystalline mass, m. p. 8°.

Acetyl-β-aldoximes.—These were prepared by dissolving the *β*-aldoxime in the minimum amount of pure acetic anhydride, warming the mixture to >30°, and then cooling it in a freezing mixture for an hour, filtering off the product, and washing it with light petroleum. The m. p.s of the compounds agreed with those previously published, except that acetyl-*β*-*p*-nitrobenzaldoxime melted at 105° and after crystallisation from benzene at 106° (Brady and McHugh, *J.*, 1925, **127**, 2414, give 96°).

Acetyl-*β*-2 : 4-dimethoxybenzaldoxime is prepared by dissolving the oxime in the minimum amount of pure acetic anhydride at 25° and shaking the solution with 2*N*-sodium carbonate, whereupon

the acetyl derivative, which is, unlike most other acetyl-β-aldoximes, not readily decomposed by this reagent, separates and crystallises from light petroleum in colourless crystals, m. p. 68—70°.

Propionyl-β-aldoximes.—These were prepared in the same way as the acetyl derivatives: *propionyl-β-p-nitrobenzaldoxime* forms pale yellow needles, m. p. 100° (Found: C, 54·2; H, 4·3. $C_{10}H_{10}O_4N_2$ requires C, 54·0; H, 4·5%), *propionyl-β-3 : 4-methylenedioxybenzaldoxime* forms a microcrystalline powder, m. p. 71° (Found: C, 59·3; H, 4·9. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0%).

Hydrolysis of Acetyl-β-aldoximes.—A weighed quantity of the acetyl derivative (1—2 g.) was added to 2N-sodium hydroxide (30 c.c.), cooled to 0°, and placed in a refrigerator for 45 minutes. At the end of that time decomposition had occurred, and the insoluble nitrile was collected, washed with water, dried, and weighed; it was subsequently identified by a m. p. and mixed m. p. determination. The alkaline solution was treated with a saturated solution of ammonium chloride, and the precipitated oxime collected, washed with a little water, dried, and weighed. No allowance was made for the slight solubility of the oximes in water so the yield of oxime is low. In the cases of acetyl-β-*p*-methyl-, acetyl-β-3 : 4-dimethoxy-, and acetyl-β-2 : 4-dimethoxy-benzaldoximes, as it was difficult to isolate the pure compounds, a weighed amount of the β-oxime was dissolved in the minimum of acetic anhydride at 25° and the solution was added to 150 c.c. of 2N-sodium hydroxide and treated as above. The amount of acetyl compound hydrolysed was calculated on the assumption that all the oxime was acetylated. As a check on this method β-*p*-methoxybenzaldoxime was treated in this way, the nitrile formed being 66·2% as against 66% when acetyl-β-*p*-methoxybenzaldoxime was hydrolysed by the first method.

Hydrolysis of Propionyl-β-aldoximes.—The method was the same as for the hydrolysis of the acetyl compounds, except that the propionyl compounds, owing to their greater stability, had to be kept in contact with the sodium hydroxide for 24 hours to ensure complete decomposition. In the cases of the propionyl derivative of β-*p*-chloro-, β-*p*-methyl-, and β-*p*-methoxy-benzaldoximes a solution of the β-aldoxime in propionic anhydride was hydrolysed, as the pure propionyl derivative could not be isolated.

Hydrolysis of Propionyl-α-aldoximes.—The propionyl derivative (0·5 g.) was treated with 2N-sodium hydroxide (75 c.c.). No appreciable action took place at room temperature in 10 minutes, so the suspension was boiled for 5 minutes, whereupon complete dissolution occurred; on cooling of the solution, no nitrile separated; the oxime was precipitated with saturated ammonium chloride solution, and the filtrate therefrom acidified and extracted with ether. The residue from the ether was examined for carboxylic acid formed by hydrolysis of nitrile, but with negative results in the cases of the propionyl-α-aldoximes described above.

Hydrolysis of Monochloroacetyl-α-aldoximes.—When carried out as above, the hydrolysis of the monochloroacetyl-α-aldoximes described gave only oxime, except in the case of monochloroacetyl-α-*o*-nitrobenzaldoxime where a small quantity of *o*-nitrobenzonitrile separated on cooling.

Hydrolysis of Trichloracetyl-α-aldoximes.—This was carried out in 2N-sodium hydroxide at 0° for 1 hour and the products were isolated as above.

Hydrolysis of n-*Heptoyl-α-aldoximes.*—The compound (1 g.) was boiled for 15 minutes with 2N-sodium hydroxide (10 c.c.), and the solution examined as before, but only the α-aldoxime was detected.

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250. *The Isomerism of the Oximes. Part XL. The Hydrolysis of Acyl Halogenobenzaldoximes by Alkalis.*

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The relative amounts of nitrile and oxime formed in the alkaline hydrolysis of (1) acetyl derivatives of the *p*-halogeno-β-benzaldoximes and (2) carbethoxy-derivatives of *o*-, *m*-, and *p*-halogeno-α-benzaldoximes have been determined.

Interpreted in the light of the mechanisms of hydrolysis, the results confirm the electronic effects of the halogens reported by Baddeley, Bennett, Glasstone, and Jones and by Bird and Ingold.

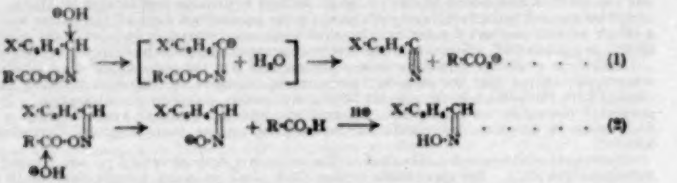
THE influence of nuclear substituents on the relative amounts of nitrile and oxime produced in the hydrolysis of an acyl-aldoxime having been established (Benger and Brady, preceding paper), it was of interest to investigate the complete series of halogenobenzaldoxime derivatives to correlate the previous results with the electronic behaviour of the halogens. By use of the technique previously described, a study has been made of the relative amounts of nitrile and oxime produced by the action of 2N-sodium hydroxide on the acetyl-β-halogenobenzaldoximes. Unfortunately only in the case of *o*-chlorobenzaldoxime and the four *p*-halogenobenzaldoximes has it been possible to prepare the β-acetyl derivatives sufficiently pure for investigation. The results are shown in Table I.

In the *para*-series F, Cl, and Br decrease the proportion of nitrile compared with the unsubstituted compound, whilst I increases it, the ratio of nitrile to oxime being in the order $F \ll Cl < Br < H \ll I$.

TABLE I.

X in β-X·C$_6$H$_4$·CH:N·OAc.	Temp.	Nitrile, %.	Oxime, %.	Total, %.	Nitrile, % of total.
p-F	0°	23	72	95	24
p-Cl	0	59	39	98	60
p-Br	0	58	33	91	64
H	0	61	30	91	67
p-I	0	90	8	98	92
p-F	25	50	45	95	53
p-Cl	25	92	3	95	97
o-Cl	0	79	11	90	88

Benger and Brady suggest that the principal mechanisms involved in the formation of nitrile and oxime at low temperatures are (1) and (2):



We will consider first the permanent polarisation due to the inductive ($-I_s$) and mesomeric ($+M$) effects which are generally accepted as being in the order F > Cl > Br > I (Baddeley, Bennett, Glasstone, and Jones, *J.*, 1935, 1827; Bird and Ingold, *J.*, 1938, 918). Now $-I_s$ would facilitate nitrile formation by mechanism (1) and oxime formation by mechanism (2), but the latter to a smaller degree as the point of attack by hydroxyl is more remote from the source of the effect; on the other hand $+M$ would retard both nitrile and oxime formation, the former probably more effectively than the latter where there is a break in the conjugation at the oxygen.

If $-I_s$ is the controlling factor, substitution by fluorine should give more nitrile than substitution by iodine; if $+M$ is the controlling factor, the effects would be the reverse. From the experimental results presence of fluorine depresses nitrile formation relative to the unsubstituted compound, so in this case $M > I_s$. On the other hand the iodo-oxime gives more nitrile than the unsubstituted oxime, so that in this case if only the above considerations are applied $I_s > M$. The positions of chlorine and bromine are less certain, as we hesitate to claim a degree of accuracy for our results which would clearly differentiate between, for example, 64 and 67% of nitrile formation.

These results are not at variance with the dissociation constants of the *p*-halogenophenols in 30% ethyl alcohol ($K_a \times 10^{10}$ = F 0·26, H 0·32, Cl 1·32, Br 1·55, I, 2·19; Bennett, Brooks, and Glasstone, *J.*, 1935, 1821) where permanent polarisation only is effective.

If it is accepted that the polarisability factor operates only at the moment of reaction to satisfy the demand of the attacking reagent it cannot retard a reaction but only favour it. The relative polarisability effects are usually accepted as being in the order I > Br > Cl > F, and as the attack is by a nucleophilic reagent they will be electron-withdrawing and more favourable to nitrile formation. The results given above show, therefore, that in the case of fluorine the inductive effect plus the polarisability factor are less than the mesomeric effect, whereas in the case of iodine the reverse holds. This conclusion is consonant with the evidence of the mesomeric moments (Groves and Sugden, *J.*, 1931, 1992) and G. N. Lewis's view that potential double-bond formation, inherent in mesomerism, is easier with the small fluorine atom than with the other halogen atoms. Pauling ("Nature of the Chemical Bond," Cornell Univ. Press, 1945, p. 236) concludes that the chlorine has about half the power of fluorine to form double bonds.

The increase in the proportion of nitrile formed in passing from the *para*- to the *ortho*-chloro-compound is to be expected from the relatively greater increase in the inductive and inductomeric effects which facilitate proton removal owing to the closer approach of the origin of the effect to the point of attack by the nucleophilic reagent.

Since acetyl-β-*p*-fluorobenzaldoxime gave on hydrolysis a smaller amount of nitrile than did acetyl-β-2 : 4- and acetyl-β-3 : 4-dimethoxybenzaldoxime it seemed probable that it would be stable, like these compounds and unlike most acetyl-β-benzaldoximes, to cold 2N-sodium

carbonate (Benger and Brady, *loc. cit.*). This proved to be the case, for no odour of nitrile was observable when acetyl-β-*p*-fluorobenzaldoxime was treated with 2N-sodium carbonate until the mixture was warmed to 50—60°.

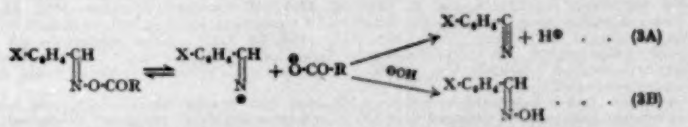
Our failure to prepare the acetyl derivatives of the β-halogenobenzaldoximes of the *ortho*- and *meta*-series led us to investigate the hydrolysis of the carbethoxy-derivatives of the α-halogenobenzaldoximes which, unlike the corresponding acetyl-α-benzaldoximes, give nitrile as well as α-oxime (Hauser, Jordan, and O'Connor, *J. Amer. Chem. Soc.*, 1935, **57**, 2456). With these compounds it was necessary to carry out the hydrolysis at higher temperatures, with the introduction of complications of interpretation which will be mentioned later. At the higher temperatures used some of the nitrile formed was hydrolysed to acid and/or amide. The results are shown in Table II. The percentage of elimination reaction, that is initial nitrile formation, was calculated from the amount of carboxylic acid, nitrile, and amide isolated.

TABLE II.

X in α-X·C_6H_4·CH:NO·O·CO_2Et.	65°. Elimination reaction, %.	65°. Oxime, %.	65°. Total, %.	100°. Elimination reaction, %.	100°. Oxime, %.	100°. Total, %.
o-F	21	78	99	40	57	97
o-Cl	35	64	99	82	16	98
o-Br	29	70	99	71	28	99
o-I	36	61	97	83	16	99
m-F	12	86	98	35	63	98
m-Cl	16	84	100	52	45	97
m-Br	16·5	83	99·5	65	34	99
m-I	19	80	99	76	21	97
p-F	6	92	98	31·5	66	97·5
p-Cl	8	90	98	42	57	99
p-Br	10	90	100	57	40	97
p-I	11	86	97	72	28	100
H	6	92	98	16	84	100

In the *para*-series, the amount of nitrile formed increases from fluorine to iodine, as with the acetyl-β-halogenobenzaldoximes, but less markedly, *p*-I/*p*-F at 65° = 1·71 and at 100° = 2·29 with the carbethoxy-α-halogenobenzaldoximes compared with *p*-I/*p*-F at 0° = 3·83 with the acetyl compounds.

The most interesting point, however, is the comparison between the decomposition of the carbethoxy-α-*p*-halogenobenzaldoximes at 65° and 100° and the corresponding acetyl-β-*p*-halogenobenzaldoximes at 0° with reference to the unsubstituted carbethoxy-α-benzaldoxime and acetyl-β-benzaldoxime under the same conditions. In the latter case fluorine depresses, and iodine favours, nitrile formation, chlorine and bromine having but small effect. In the former case at 65° fluorine has little effect whilst chlorine, bromine, and iodine slightly facilitate nitrile formation, but at 100° all the halogens markedly facilitate nitrile formation. This may be due to a differential temperature coefficient affecting the opposing electronic displacements, or to the third mechanism of decomposition of acyl aldoximes suggested by Benger and Brady (*loc. cit.*) coming into operation at the higher temperatures (cf. Ambrose and Brady, *J.*, 1950, 1243).



As the oxime obtained from the carbethoxy-derivative is the stable α-isomeride this mechanism cannot be eliminated as it was in the alkaline hydrolysis of the acetyl-β-aldoximes (cf. Benger and Brady, *loc. cit.*). This mechanism will be favoured by the mesomeric effect of the halogens, and if it leads mainly to nitrile (3A) the proportion of nitrile to oxime in the decomposition of the fluoro-compound might well be greater than in the unsubstituted carbethoxy-derivative. This problem is being further investigated.

In the *meta*-series the amount of nitrile formed increases from fluorine to iodine at both temperatures and is greater than in the *para*-series. In this case the electromeric effect of the halogen will be much less marked and the inductive and inductomeric effects will be enhanced

compared with the *para*-substituted compounds because of the closer approach of the seat of the effect to the point of reaction. In the *ortho*-series a still greater amount of nitrile is produced at both temperatures owing to the still closer approach of the source of the inductive and inductomeric effects. The retarding mesomeric effect may be less effective in the case of the *ortho*-substituted compounds as it has been suggested that for reasons of symmetry the mesomeric effect will be relayed more powerfully to the *para*- than to the *ortho*-position (Waters, *Trans. Faraday Soc.*, 1941, **37**, 746).

In this series although the fluoro-compound gives least nitrile and the iodo-compound gives most, the behaviour of the chloro-compound is anomalous, as it gives more nitrile than the bromo-compound. This abnormal behaviour of chlorine, especially in the *ortho*-position, is not unknown; it appears, for example, in the action of potassium iodide on the halogenobenzyl chlorides (Bennett and Jones, *J.*, 1935, 1815).

Experimental.

o-Fluorobenzaldoximes.—The *o*- and *p*-fluorobenzaldoximes were obtained by preparing the aldehydes by the method of Rinkes (*Chem. Weekbl.*, 1919, **16**, 206) by chlorination of the fluorotoluenes and hydrolysis. The mixture of aldehyde and alcohol so obtained was not separated, but treated with aqueous hydroxylamine hydrochloride and enough 4*N*-sodium hydroxide to form the soluble sodium salt of the oxime; the fluorobenzyl alcohol was removed by extraction with a mixture of benzene and light petroleum, and the oxime precipitated from the aqueous layer with carbon dioxide. Rinkes gives no yields, but from 70 g. of fluorotoluene 44—50 g. of oxime were obtained.

o-Fluorobenzaldoxime, after crystallisation from light petroleum, melts at 64·5—65° (Found: C, 60·2; H, 4·5. C_7H_6ONF requires C, 60·4; H, 4·3%), and *p-fluorobenzaldoxime* at 88·5° (Found: C, 60·4; H, 4·3%). Rinkes gives m. p.'s 62·6° and 81·2° respectively and publishes no analyses, but his method of preparation of the oximes would not eliminate fluorobenzoic acids, and it has been found that small quantities of these depress the m. p. of the oximes and are not readily removed by crystallisation from light petroleum.

m-Fluorobenzaldehyde has not been previously described and has been prepared as follows. *m*-Nitrobenzaldehyde (50 g.), suspended in concentrated hydrochloric acid (250 c.c.), was reduced with stannous chloride (225 g.), and the reddish-brown solution was cooled to 0°, diluted with water (50 c.c.), and diazotised with sodium nitrite (23 g. in 100 c.c. water). The yellowish-brown solution containing a slight deposit of amorphous material which need not be removed was kept for 30 minutes, and powdered ice was then added (100 g.), followed by borofluoric acid (100 c.c.); the diazonium borofluoride soon separated as brownish needles and was washed with water, alcohol, and ether and dried over concentrated sulphuric acid in a vacuum. The diazonium borofluoride, mixed with an equal bulk of sand, was decomposed in 2 portions in a flask fitted with a long condenser tube leading to a stoppered bottle connected to a water-pump. After evacuation, decomposition was started by heating the flask at one point. The boron trifluoride evolved dissolved in the pump water, and a greenish crystalline sublimate appeared in the condenser and was driven over into the receiver. When stronger heating was applied, an oil distilled. On addition of water to the contents of the receiver, the solid portion decomposed, with the liberation of boron trifluoride. The oil was purified by conversion into the oxime by the addition of hydroxylamine hydrochloride (15 g. in water) and enough 2*N*-sodium hydroxide to give a clear solution. After cooling and filtration, the solution was saturated with carbon dioxide, and the precipitated oxime (15 g.) collected, dried, and crystallised from light petroleum containing a little benzene. The oxime (10 g.) was heated in steam with *N*-hydrochloric acid (100 c.c.), the aldehyde distilling as a colourless oil which was extracted with ether. *m-Fluorobenzaldehyde* is a colourless liquid with a benzaldehyde-like odour, b. p. 170°/760 mm. (Found: C, 67·4; H, 4·0. C_7H_5OF requires C, 67·7; H, 4·0%); on oxidation it gave *m*-fluorobenzoic acid, m. p. 123° (Kuhn and Wassermann, *Helv. Chim. Acta*, 1928, **11**, 31). The aldehyde was re-oximated as before and *m-fluorobenzaldoxime* crystallised from light petroleum as colourless prisms, m. p. 67—67·5° (Found: C, 61·1; H, 4·3. C_7H_6ONF requires C, 60·4; H, 4·3%).

o-Chloro-, o-Bromo-, and o-Iodo-benzaldoximes.—*o*-Bromo- and *o*-iodo-benzaldehyde were prepared by a Sandmeyer reaction (Stuart, *J.*, 1888, **53**, 1401; Weitzenbock, *Monatsh.*, 1913, **34**, 206) from *o*-aminobenzaldehyde prepared by the reduction of *o*-nitrobenzaldehyde with hydrogen using a nickel catalyst (Ruggli and Schmid, *Helv. Chim. Acta*, 1935, **18**, 1235). These authors do not specify the nature of the catalyst, but it was found that Raney nickel kept in contact with the alkaline sodium aluminate solution overnight was suitable: the more active form promoted a rapid reduction to *o*-aminobenzyl alcohol.

m-Bromo- and *m*-iodobenzaldehyde were obtained from *m*-aminobenzaldehyde, and *p*-bromo- and *p*-iodobenzaldehydes were prepared from the *p*-aminobenzaldehyde "polymer" (Willgerodt and Ucke, *J. pr. Chem.*, 1912, **86**, 276). The *o*-bromobenzaldoximes were prepared by adding the aldehyde to an equivalent amount of hydroxylamine hydrochloride in water to which three equivalents of 2*N*-sodium hydroxide had been added with cooling, and precipitating the oxime with carbon dioxide. The iodobenzaldoximes were prepared by Patterson's method (*J.*, 1896, **69**, 1006). *o-m*-Bromobenzaldoxime melted at 74—75°; Einhorn and Germsheim (*Annalen*, 1895, **284**, 141) give m. p. 71·5°. The *o*-chlorobenzaldoximes were prepared in the same way as the *o*-bromobenzaldoxime from purchased chlorobenzaldehydes. Except where specially mentioned, the m. p.s of the oximes were those given by previous workers.

β-Halogenobenzaldoximes.—The *β*-oximes of the *para*-series were prepared by dissolving the *α*-oxime in hot dry benzene, precipitating the hydrochloride with dry hydrogen chloride, collecting, drying, and decomposing the salt with excess of 2*N*-sodium carbonate. *β-p*-Fluorobenzaldoxime melted at 120—121°; Rinkes (*loc. cit.*) gives m. p. 116—117°.

This method was not successful with the *ortho*- and *meta*-compounds, but when the hydrogen chloride was replaced by hydrogen bromide, prepared by dropping fuming hydrobromic acid on phosphoric oxide and dried by passage through a U-tube containing phosphoric oxide, conversion was brought about. So prepared, β-*o*-chlorobenzaldoxime melted at 100°. Brady and McHugh (*J.*, 1924, **125**, 547) obtained a compound of this m. p. by the action of ultra-violet light on the α-isomeride, but Brady, Cosson, and Roper (*J.*, 1925, **127**, 2427), using the hydrochloride method, obtained a product melting at 101—103°. β-*o-Iodobenzaldoxime*, obtained for the first time by this method and crystallised from benzene, had m. p. 135° (Found: C, 34·3; H, 2·3. C_7H_6ONI requires C, 34·0; H, 2·4%). β-*m*-Iodobenzaldoxime (from benzene), m. p. 121°, and β-*m*-fluorobenzaldoxime (from light petroleum containing a little benzene), m. p. 103—104°, have also been obtained for the first time by this method.

The decomposition of the hydrobromide from α-*o*-fluorobenzaldoxime with ice-cold 2N-sodium carbonate and crystallisation from benzene gave a product, m. p. 57—62°, which gives an intense red colour with alcoholic ferric chloride, a diagnostic test for β-aldoximes (Beck and Hass, *Annalen*, 1907, **355**, 37). When dissolved in acetic anhydride and warmed with sodium carbonate, a strong odour of nitrile was produced. Addition of an equal amount of α-*o*-fluorobenzaldoxime (m. p. 64—65°) depressed the m. p. to <30°. The compound undoubtedly consists largely of the β-isomeride, but is probably not pure in view of the range over which it melts; further crystallisation lowered the m. p. β-*o*-Methoxybenzaldoxime has never been isolated pure, and, as the methoxy- and fluoro-substituents have in common a large mesomeric displacement, the difficulty in obtaining pure β-*o*-fluorobenzaldoxime is not surprising.

A quicker method of obtaining the β-isomerides from *o*-iodo-, *m*-iodo- and *m*-fluoro-α-aldoximes consists in dissolving these in the minimum amount of warm ether and adding a slight excess of hydrobromic acid (*d* 1·7) from a measuring pipette. Crystals of hydrobromide soon separate, and the mixture solidifies with evolution of heat and some ether boils off; the rest is removed in a current of dry air, and the addition of 2N-sodium carbonate liberates the β-aldoxime. The crude material so obtained is, however, not very pure and the yield of pure β-aldoxime obtained from it by crystallisation is not as high as when gaseous hydrogen bromide is used.

β-Acetyl-halogenobenzaldoximes.—These were prepared by the method of Hauser and Sullivan (*J. Amer. Chem. Soc.*, 1933, **55**, 4611). It is essential that the acetic anhydride should be free from traces of acetyl chloride or hydrogen chloride, and acid fumes and bright light should be excluded during the preparation. The compounds are very unstable and must be prepared immediately before use. The acetyl derivatives of the β-aldoximes frequently melt at tesnperatures close to those of the α-aldoximes, so in order to be sure that inversion had not occurred during the preparation, mixed m. p.s were determined with samples of the acetyl-α-aldoxime; in every case there was a depression of >20°.

Acetyl-β-*p*-fluorobenzaldoxime has m. p. 82—83°, acetyl-β-*p*-iodobenzaldoxime m. p. 76—77°, and acetyl-β-*o*-chlorobenzaldoxime, m. p. 45—46°. The acetyl derivatives of β-*p*-chlorobenzaldoxime and β-*p*-bromobenzaldoxime have been previously described; our specimen of the latter melted at 69—70°, though Hantzsch (*Z. physikal. Chem.*, 1894, **13**, 520) gives 91—92°. Acetyl derivatives of β-*o*-bromobenzaldoxime and β-*o*-iodobenzaldoxime could not be obtained pure, as mixtures of the α- and β-isomerides were always formed; the *m*-halogeno-β-benzaldoximes gave mainly nitrile. Hantzsch (*loc. cit.*) experienced similar difficulties with these compounds.

Carbethoxy-α-halogenobenzaldoximes.—The following O-*carbethoxy-halogenobenzaldoximes* were prepared by the method of Brady and Dunn (*J.*, 1916, **109**, 678) who describe the carbethoxy-α-chlorobenzaldoximes: o- (from light petroleum), m. p. 41—42° (Found: C, 57·6; H, 4·9. $C_{10}H_{10}O_3NF$ requires C, 56·9; H, 4·9%), m- (from light petroleum), m. p. 37—39° (Found: C, 57·2; H, 4·9%), and p-*fluoro*- (from aqueous alcohol), m. p. 76—77° (Found: C, 57·3; H, 5·0%); o- (from light petroleum and benzene), m. p. 78° (Found: C, 44·5; H, 4·0. $C_{10}H_{10}O_3NBr$ requires C, 44·2; H, 3·7%), m- (from light petroleum and benzene), m. p. 46—48° (Found: C, 44·5; H, 3·8%), and p-*bromo*- (from aqueous alcohol), m. p. 90—91 (Found: C, 44·2; H, 3·7%); o- (from aqueous alcohol), m. p. 109·5° (Found: C, 38·1; H, 3·1. $C_{10}H_{10}O_3NI$ requires C, 37·6; H, 3·1%), m- (from light petroleum), m. p. 59—61° (Found: C, 38·0; H, 3·3%), and p-*iodo*- (from aqueous alcohol), m. p. 93—94° (Found: C, 37·9; H, 3·1%).

Hydrolysis of Acetyl-β-halogenobenzaldoximes.—The pure, freshly prepared, acetyl derivative (1 g.) was added to 2N-sodium hydroxide (15 c.c.) previously cooled to 0° or heated in a thermostat to 25°. After 120 minutes at 0° or 45 minutes at 25°, with frequent shaking, the acetyl derivative was completely decomposed to nitrile and oxime, the latter dissolving in the excess of sodium hydroxide. The nitrile was collected in a tared sintered-glass crucible, the filtrate saturated with carbon dioxide, and the precipitated oxime likewise collected. After being washed with water the solids were dried in a desiccator to constant weight. No indication of the formation of carboxylic acid by hydrolysis of the nitrile was detected and no correction was made for the slight solubility of the compounds in water. The m. p.s of the products were taken to ascertain whether α- or β-aldoximes were recovered. The crude nitriles melted as follows: *p*-F- 33° (34·8°); *p*-Cl- 89—91° (91—92°); *p*-Br 108—110° (113°); *p*-I- 122° (124°); *o*-Cl- 45° (45°); the figures in brackets are the m. p.s of the nitriles recorded in the literature. In the following list the m. p. of the oxime recovered is given followed by the correct m. p.s of the β- and α-oximes: *p*-F- 115—118°, β- 121°, α- 87°; *p*-Cl- 134—138°, β- 149°, α- 108°; *p*-Br- 150°, β- 157°, α- 115°; *p*-I- 148°, β- 150°, α- 119°; *o*-Cl- 87—95°, β- 110°, α- 75—76°. The relative amount of nitrile and oxime produced are shown in Table I.

Hydrolysis of Carbethoxy-α-halogenobenzaldoximes.—The hydrolyses were carried out at 65° and 100°. In the first case a rubber-stoppered flask (50 c.c.) containing 2N-sodium hydroxide (15 c.c.) was heated at 65° (thermostat) and the carbethoxy-compound (1 g.) introduced. The mixture was shaken periodically until complete dissolution occurred (1—3 days); in these circumstances the insoluble nitrile first formed is hydrolysed to the corresponding acid; it was more satisfactory to adopt this procedure than to heat for a shorter time and determine the nitrile and acid separately. For experiments at 100°, the 2N-sodium hydroxide (15 c.c.) and the carbethoxy-compound (1 g.) were introduced into a small bulb (30—40 c.c.), which was sealed, weighted with lead, and submerged in boiling water. The bulbs

were shaken during the first few minutes and then left for 45 minutes; in this instance some nitrile remained insoluble, contaminated in some cases with a small amount of amide.

In the reactions at 65° the cooled solution was diluted to 30 c.c. with water, saturated with carbon dioxide, and the precipitated oxime collected in a tared sintered-glass crucible, washed with a little water, dried, and weighed. The filtrate and washings were extracted once with ether to remove dissolved oxime, the ethereal solution, after washing, evaporated in a tared beaker, and the oxime dried in a desiccator and weighed. The aqueous solution was acidified with hydrochloric acid and the carboxylic acid extracted twice with ether; the ethereal extracts were washed with a little water and evaporated in a tared beaker, and the residue dried in a desiccator and weighed.

When the reaction was carried out at 100°, the cooled solution was extracted with ether, which removed nitrile and some oxime, the latter was removed by washing the ethereal extracts twice with small quantities of 2*N*-sodium hydroxide. The alkaline solution and washings were saturated with carbon dioxide, and the precipitated oxime was collected or extracted with ether according to its amount; when it was collected, the filtrate was extracted with ether. The hydrogen carbonate solution was acidified and the carboxylic acid extracted with ether. The various ethereal solutions were evaporated in tared beakers, and the products dried and weighed. In no case was the recovery less than 97% calculated on the material used.

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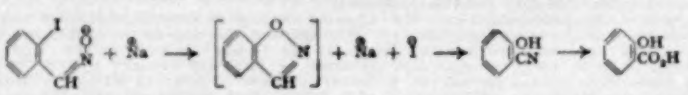
251. *The Isomerism of the Oximes. Part XLI. The Action of Alkali on α- and β-o-Iodobenzaldoximes.*

By O. L. BRADY and S. G. JARRETT.

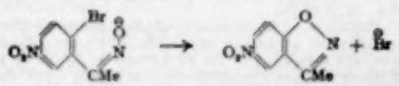
The relative rates of decomposition of α- and β-*o*-iodobenzaldoximes by alkali to salicylonitrile are approximately 1 : 10. This confirms the results obtained by Brady and Bishop with the α- and β-2-chloro-5-nitrobenzaldoximes, from which these authors adduced the *anti*-configuration for the β-benzaldoximes.

In the case of β-*o*-iodobenzaldoxime only, a secondary reaction takes place involving the transformation of about 50% of the oxime into *o*-iodobenzamide.

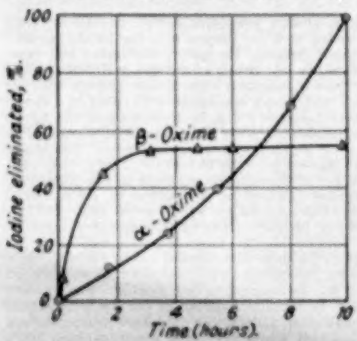
BRADY, COSSON, and ROPER (*J.*, 1925, **127**, 2427) observed that α-*o*-iodobenzaldoxime, when boiled with excess of 30% sodium hydroxide solution, lost iodine with the formation of salicylic acid. The reaction was supposed to involve the formation of an unstable *iso*oxazole:



With 2-bromo-5-nitroacetophenone oxime the *iso*oxazole, being incapable of tautomeric change, can be isolated (Meisenheimer, Zimmermann, and Kummer, *Annalen*, 1926, **446**, 207).



Rates of elimination of iodine by the o-iodobenzaldoximes in 2N-sodium hydroxide at 64°.

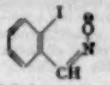


These authors proposed to investigate the rates of elimination of iodine from the α- and β-isomerides to confirm the results obtained with α- and β-2-chloro-5-nitrobenzaldoximes by Brady and Bishop (*J.*, 1925, **127**, 1357), but they were unable to prepare β-*o*-iodobenzaldoxime. We have now prepared this isomeride.

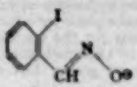
When the α- and β-*o*-iodobenzaldoximes were heated at 65° with 2*N*-sodium hydroxide the α-isomeride slowly eliminated iodine completely; the β-isomeride lost iodine more rapidly but the liquid soon became turbid and crystals of *o*-iodobenzamide slowly formed. The rates of elimination are shown in the figure; only a little more than 50% of the theoretical amount of iodine

was eliminated from the β-isomeride. Elimination of iodine was about ten times as fast from the β- as from the α-isomeride.

These results confirm those of Brady and Bishop that, if *iso*xazole formation occurs most easily when the anionic oxygen is nearest to the halogen, the β-oxime must have the *anti*-configuration.

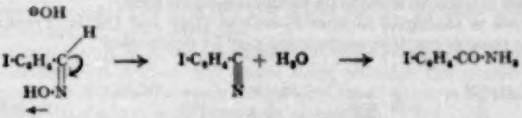


β-Oxime anion.



α-Oxime anion.

With the β-aldoxime two simultaneous reactions occur: attack by the oximino-anion on the nuclear carbon atom bearing iodine, leading to isoxazole formation; and attack by a hydroxyl ion on the methine-hydrogen atom, with simultaneous elimination of the hydroxyl group attached to nitrogen:



As in the case of the acetyl derivatives the methine-hydrogen atom is more readily removed from the β- than from the α-isomeride, so that the second reaction is observed only in this case. *o*-Iodobenzaldoxime, therefore, supplies another example of nitrile formation direct from the oxime under the influence of hydroxyl ions, but, unlike the previous one, *o*-nitrobenzaldoxime (Reissert, *Ber.*, 1908, **41**, 3815; Brady and Goldstein, *J.*, 1926, 1918), only the β-isomeride undergoes this reaction. This is understandable since iodine will be less effective than the nitro-group in facilitating the attack by hydroxyl ions on the methine-hydrogen atom.

Experimental.

α-*o*-Iodobenzaldoxime (m. p. 107—108°) was prepared by the method of Patterson (*J.*, 1896, **69**, 1006) from *o*-iodobenzaldehyde prepared from *o*-aminobenzaldehyde (Weitzenbock, *Monatsh.*, 1913, **34**, 206). β-*o*-Iodobenzaldoxime (m. p. 135°) was obtained by using hydrogen bromide in place of hydrogen chloride in the usual conversion (Brady and Jarrett, *J.*, 1950, 1227).

Action of Sodium Hydroxide.—The α- and β-oximes (2·47 g. = N/10) were each dissolved in 2N-sodium hydroxide (100 c.c.) and heated at 65° (thermostat). At intervals samples (10 c.c.) were removed, added to ice-cold N-nitric acid (25 c.c.), N/10-silver nitrate (10 c.c.) was added, and the excess titrated with N/10-ammonium thiocyanate.

In the case of the β-isomeride a turbidity soon appeared in the solution, and later long crystals formed which were identified as *o*-iodobenzamide by the usual means (Found: C, 34·1; H, 2·7. Calc. for C_7H_6ONI: C, 34·0; H, 2·4%).

If the reaction is of the first order, the rate constant for the formation of iodide from the α-aldoxime was *k* (after 100 min.) 0·00121, (after 335 min.) 0·00146, and (after 480 min.) 0·0025, and for the β-aldoxime (after 10 min.) 0·0106, (after 25 min.) 0·0233, and (after 90 min.) 0·0084. As might be expected the results for the β-aldoxime are poor but the figures indicate the relative speeds of the two reactions. With the β-aldoxime between 90 and 285 min. the amount of iodine eliminated increased only from 53·0 to 55·0%, and then ceased.

The other product of the reaction with both isomerides was salicylonitrile, which was isolated from the alkaline solutions by the addition of dilute sulphuric acid and extraction with ether. Attempts to avoid amide formation by varying the concentration of the alkali and the temperature of the solution were unsuccessful.

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252. *The Isomerism of the Oximes. Part XLII. The Acid Hydrolysis of Acetyl-α-aldoximes.*

By O. L. Brady and J. Miller.

The acid-catalysed hydrolysis of nuclear substituted acetyl-benzaldoximes in aqueous acetone has been shown to take place by a bimolecular mechanism involving acyl–oxygen fission.

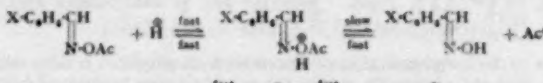
The rate constants for the reaction for varying nuclear substituents differ by only small amounts, as might be expected from the remoteness of the point of action from the electron-controlling substituent group, but are in the order *p*-OMe > *p*-Me > *o*-OMe > *m*-NO_2 > *p*-NO_2 > *o*-NO_2.

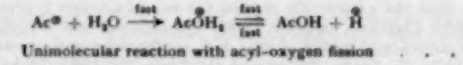
A secondary, but much slower, reaction between hydrogen chloride and acetone has been shown to take place when the concentration of water in the acetone is below 4%.

A study has been made of the acid-catalysed hydrolysis of some substituted acetyl-α-benzaldoximes, X·C_6H_4·CH:N·OAc, in aqueous acetone.

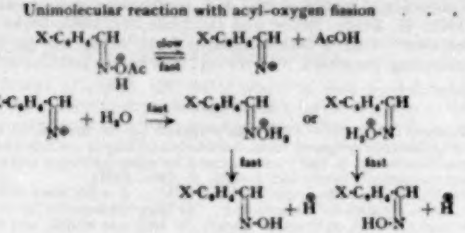
The possibility of neutral hydrolysis was first eliminated by showing that no appreciable hydrolysis occurred in aqueous acetone under the conditions used.

If the hydrolysis is analogous to ester hydrolysis (Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686) the possible reaction mechanisms may be represented:



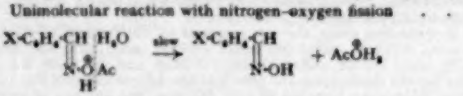


Unimolecular reaction with acyl–oxygen fission . . . . . (A′ 1)

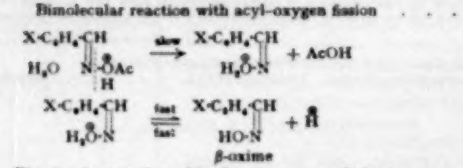


(this is analogous to alkyl–oxygen fission in the hydrolysis of esters)

Unimolecular reaction with nitrogen–oxygen fission . . . . . (A″ 1)



Bimolecular reaction with acyl–oxygen fission . . . . . (A′ 2)



Bimolecular reaction with nitrogen–oxygen fission . . . . . (A″ 2)

Of these possible mechanisms those involving nitrogen–oxygen fission, A″ 1 and A″ 2, can be eliminated on the following grounds. Only the α-oxime is produced in the hydrolysis; though the α-oxime is the more stable of the isomerides, the β-hydrochloride formed as an inter-

mediate is more stable than the α-hydrochloride, and under the experimental conditions one would expect to be able to isolate some β-oxime if mechanisms A″ 1 or A″ 2 were operative. In absolute methyl alcohol acid-catalysed hydrolysis gives exclusively oxime and not the *O*-methyl ether as would be demanded by nitrogen–oxygen fission.

$$X\text{-}C_6H_4\text{-}CH{:}\overset{\oplus}{N} + HOMe \longrightarrow X\text{-}C_6H_4\text{-}CH{:}N\text{-}\overset{\oplus}{O}HMe \rightleftharpoons X\text{-}C_6H_4\text{-}CH{:}N\text{-}OMe + \overset{\oplus}{H} \quad \text{from A″ 1}$$

$$X\text{-}C_6H_4\text{-}CH{:}N\text{-}\overset{\oplus}{O}HAc \longrightarrow X\text{-}C_6H_4\text{-}CH{:}N\text{-}\overset{\oplus}{O}HMe + AcOH$$

$$\uparrow \text{MeOH} \qquad \downarrow$$

$$X\text{-}C_6H_4\text{-}CH{:}N\text{-}OMe + \overset{\oplus}{H} \quad \text{from A″ 2}$$

Finally it would be expected that varying the substituent X in the benzene ring from, for example, nitro to methoxy, or replacing the methine-hydrogen atom by methyl would have a substantial effect on the rate constant, whereas, in fact, although an effect is observed it is small and is reasonably explicable by the influence of the substituents on the basicity of the oxygen atom at which proton is added (compare Day and Ingold, *loc. cit.*, for effect of electron-accession or -withdrawal in carboxylic ester hydrolysis).

It is not possible to decide from the experimental kinetics between the unimolecular and the bimolecular mechanism with acyl–oxygen fission since, although the kinetics are those for a first-order reaction, even in 99·5% acetone the initial ratio of water to acetate is not less than 6 : 1 and the bimolecular reaction is not, therefore, eliminated.

Other evidence is, however, in favour of a bimolecular mechanism. No mass-law effect was detected, such as would be expected in the unimolecular reaction; on the other hand "*ortho*-effects" were observed. The activation energies (14,000—18,000 cals./g.-mol.) are reasonable for a bimolecular, but low for a unimolecular, reaction and finally it seems unlikely that a reaction involving the separation of the cation would increase in velocity in acetone solution with decreasing amounts of water down to 2% (Table II). Mechanism A′ 2 seems, therefore, to be the correct one.

In the actual measurement of the rate constants certain complications arose. The oxime produced by the hydrolysis of the acetyl derivative undergoes further hydrolysis to aldehyde and hydroxylamine:

$$X\text{-}C_6H_4\text{-}CH{:}N\text{-}OH + H_2O \rightleftharpoons X\text{-}C_6H_4\text{-}CHO + NH_2\text{-}OH$$

The rate of this secondary reaction was about one-fifth to one-tenth of the rate of the hydrolysis of the acetyl derivative, even with the highest acid concentrations used.

After 24 hours at 25° with 0·4N-hydrochloric acid in 80% acetone acetyl-α-*m*-nitrobenzaldoxime yielded 40—45% of α-*m*-nitrobenzaldoxime and 50—55% of *m*-nitrobenzaldehyde, whereas under these conditions the acetate is completely hydrolysed. After only 3½ hours very little aldehyde was formed, although the acetyl compound was practically completely hydrolysed.

The formation of acetic acid was followed by titration with barium hydroxide using phenolphthalein, and it was found that hydroxylamine hydrochloride titrated as the equivalent of hydrochloric acid under these conditions, so that the secondary reaction is not evident in the measurements though it may have some effect towards the end of the primary reaction owing to competition for proton between the hydroxylamine and the acetyl compound.

A further complication arose with reactions carried out in solutions containing a high percentage of acetone (>96%) owing, it is suggested, to the slow formation of mesityl oxide and phorone and combination of these compounds with the hydrogen chloride, thus reducing its effective concentration. This reaction has been shown to occur, not only in the presence of the acetyl-aldoximes, but also in the solutions of hydrogen chloride in acetone and water alone. The rate of this reaction is only one-fiftieth to one-hundredth of the rate of hydrolysis of the acetyl compound and a small correction can be applied where necessary to the titration values of the primary hydrolysis.

In all cases k has been calculated from the equation

$$k = \frac{1}{t}\ln\frac{a}{a-x} = \frac{2{\cdot}303}{t}\log\frac{a}{a-x}$$

Table I indicates the effect of different substituents in the benzene nucleus.

TABLE I.

80% Acetone,* $k \times 10^5$ in secs.$^{-1}$.

X in X·C_6H_4·CH:N·OAc.	0·05*N*-HCl.	0·102*N*-HCl.	0·204*N*-HCl.	0·409*N*-HCl.
o-NO_2	—	1·537	—	6·226
p-NO_2	—	1·731	—	—
m-NO_2	0·901	1·916	3·834	9·707
o-OMe	—	2·004	—	9·20
p-Me	—	2·031	—	10·11
3 : 4-CH_2O_2	—	—	4·491	—
p-OMe	—	2·827	4·597	11·12
(*m*-NO_2·C_6H_4·CMe:N·OAc)	—	—	—	10·93

* 80% Acetone and similar expressions indicate a mixture prepared by mixing 80 parts by volume of anhydrous acetone with 20 parts by volume of an appropriate mixture of hydrochloric acid and water to give a solution of the required normality with respect to hydrochloric acid, alteration in volume on mixing being ignored.

It will be seen that the effect of passing from groups of such different electron displacements as *p*-NO_2 to *p*-OMe produces but a small difference in rate constant.

The rate constants are in the order, *p*-OMe > *p*-Me > *o*-OMe > *m*-NO_2 > *p*-NO_2 > *o*-NO_2, with the value for *o*-OMe not much higher than for *m*-NO_2; the value for *o*-NO_2 is considerably less than that for *p*-NO_2. The acid dissociation constants of the α-aldoximes at 25° in water are in the order, *p*-OMe < *o*-OMe < 3 : 4-CH_2O_2 < *m*-NO_2 < *o*-NO_2 < *p*-NO_2 (Brady and Goldstein, *J.*, **1926**, 1918) and the basicity constants must run in the reverse order. If it be accepted that the effect of the substituent on the basicity of the oxime, *i.e.*, the oxime's attraction for proton, is paralleled in the acetyl derivatives, the rate constant for the hydrolysis of the latter compounds increases with increased affinity for proton if one excepts the *o*-compounds. The rate constants for the hydrion-catalysed hydrolysis of substituted benzyl acetates are *p*-Me > *p*-NO_2 > *m*-NO_2 (Tommila and Hinshelwood, *J.*, **1938**, 1801) but, on the other hand, those for the hydrolysis of substituted ethyl benzoates are in the order *o*-NO_2 ≪ *p*-OMe < *p*-Me < *m*-NO_2 < *p*-NO_2 (Timm and Hinshelwood, *J.*, **1938**, 862).

In the former case the mechanism is much more nearly parallel with the hydrolysis of the acetyl oximes:

$$\mathrm{X{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}\overset{\oplus}{O}HAc} \xrightarrow{H_2O} \mathrm{X{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}OH + H_2\overset{\oplus}{O}Ac} \quad \text{(i)}$$

$$\mathrm{X{\cdot}C_6H_4{\cdot}CH_2{\cdot}\overset{\oplus}{O}HAc} \xrightarrow{H_2O} \mathrm{X{\cdot}C_6H_4{\cdot}CH_2{\cdot}OH + H_2\overset{\oplus}{O}Ac} \quad \text{(ii)}$$

$$\mathrm{X{\cdot}C_6H_4{\cdot}CO{\cdot}\overset{\oplus}{O}HEt} \xrightarrow{H_2O} \mathrm{X{\cdot}C_6H_4{\cdot}CO{\cdot}\overset{\oplus}{O}H_2 + HOEt} \quad \text{(iii)}$$

In (i) and (ii) electron-recession due to X will hinder oxonium-salt formation but is not likely, when X is in the *p*-position, to have much effect on the approach of the water molecule to the acetyl centre. In (iii), however, electron-recession, while hindering oxonium-salt formation, will exert a very favourable influence on the approach of the water molecule to the carbon atom directly attached to the nucleus. The *p*-nitro-group will accordingly hinder hydrolysis of acetyl-oximes and benzyl acetates, but favour hydrolysis of ethyl benzoates. The contrary effects will be observed with the methyl and the methoxy-group, though in the latter case some reservation may be necessary owing to the tendency of oxonium-salt formation by this group with a resulting inversion of its electronic effect.

There is a small "*ortho*-effect" since the reaction with the *o*- is slower than with the *p*-nitro-compound, and the dissociation constants of the aldoximes would lead one to expect the reverse order; further, it is slower with the *o*-methoxy-compound than one would expect from the dissociation constant which is only about 8% above that of the *p*-analogue. As, however, the point of attack by the water molecule is much more remote from the *ortho*-position in the acetyl-oximes than in the ethyl benzoates one does not get the very pronounced slowing effect of the *o*-nitro-group that one finds in the latter series where the rate constant is depressed below that of the *p*-methoxy-ester.

A comparison between the rate constants for acetyl-*m*-nitrobenzaldoxime and acetyl-*m*-nitroacetophenone oxime shows that the effect of replacing the methine-hydrogen atom by

methyl is to increase the rate constant, as might be expected from the electronic effect of the methyl group weakening the acid dissociation constant or increasing the basic dissociation constant and facilitating attachment of proton. The acid dissociation constants of α-benzaldoxime and acetophenone oxime are approximately as 6·3 : 1 (Brady and Chokshi, *J.*, 1929, 946).

TABLE II.

0·204N-HCl. $k \times 10^5$ in secs.$^{-1}$.

X in X·C$_6$H$_4$·CH:N·OAc.	80% Acetone.	90% Acetone.	96% Acetone.	98% Acetone.	99·5% Acetone.
o-NO$_2$	(3·074)	—	—	12·08	—
m-NO$_2$	3·834	5·266	11·85	15·14	4·779
o-OMe	(4·006)	—	—	20·0	—
p-Me	(4·062)	—	—	18·32	—
p-OMe	4·597	6·952	16·67	20·36	—

Figures in parenthesis are calculated by doubling the constant for 0·1N-HCl in Table I. The rate constants in 98 and 99·5% acetone are corrected for phorone formation.

TABLE III.

$k \times 10^5$ in secs.$^{-1}$.

	0·102N-HCl.			0·14N-HCl.
	80% Acetone.	98% Acetone.	99% Acetone.	99·5% Acetone.
m-NO$_2$	1·916	6·938 *	5·312 *	3·533 *

* Corrected for phorone formation.

Tables II and III show the effect on the rate constant of altering the concentration of water. Decreasing the water content of the solution from 20% to 2% causes a rate increase, slowly at first, then more rapidly, and finally more slowly. A further decrease in water content down to 0·5% produces a marked decrease in the rate.

The ratio of the rate in 80% acetone to that at other concentrations, with 0·2N-hydrochloric acid, for acetyl-α-*m*-nitrobenzaldoxime is 80% 1, 90% 1·37, 96% 3·09, 98% 3·95, and 99·5% 1·25, and for acetyl-α-*p*-methoxybenzaldoxime is 80% 1, 90% 1·51, 96% 3·63, and 98% 4·43.

At very low water concentration the hydrogen chloride is little ionised and the rate constant is low. Brownson and Cray (*J.*, 1925, **127**, 2923) found that the ionisation of 0·1N-hydrochloric acid in aqueous acetone fell from 47·2% to 19·8% when the water content fell from 20% to 10%, and that of 0·02N-hydrochloric acid from 66·8% to 17·6% when the water content fell from 20% to 5%.

Passing from 0·5% to 2% of water considerably increases the ionisation of the hydrochloric acid and a rapid increase in the rate constant occurs but, with >2% of water, a competition effect between water molecules and the acetyl compound for available protons causing a rate reduction begins to outweigh the still increasing concentration of hydrogen ions. Thus the drop for 2% to 4% of water is small, but as the rate of increase of dissociation drops, the competition effect shows more strongly in solutions containing 4—10% of water.

Above 10% of water the competition shows a " saturation " effect decreasing the relative influence of increasing water concentration.

The rate constants are independent of the concentration of the acetyl compound (in 80% acetone with 0·2N-hydrochloric acid, 0·0475M-acetyl-α-*m*-nitrobenzaldoxime $k = 3{\cdot}830 \times 10^{-4}$ secs.$^{-1}$, 0·0931M-acetyl-α-*m*-nitrobenzaldoxime $k = 3{\cdot}792 \times 10^{-4}$ secs.$^{-1}$), and, as can be seen from Table I, are approximately proportional to the concentration of hydrochloric acid though in the stronger acid there is a marked " over-acid effect."

Since the hydrogen-ion concentration cannot be identified with the concentration of hydrogen chloride in these solutions the former has been determined potentiometrically by using the platinum–quinhydrone electrode and standard procedure. A 0·0028N-hydrochloric acid solution in 80% acetone was used as reference solution and its pH was estimated from the data of Brownson and Cray (*loc. cit.*) to be 2·73. By use of the formula $pH = E/0{\cdot}0591$ the following data for solutions of hydrogen chloride in 80% acetone at 25° were obtained :

Normality of HCl	0·051	0·102	0·205	0·409
E (mv.)	74·5	84	95	107
H$^+$ activity, moles/l.	0·0337	0·0486	0·0745	0·1190

These were confirmed by intercomparison of the half-cells.

Conductivities of hydrogen chloride in 80% acetone at 25° were measured by using the normal procedure with the following results :

Normality of HCl	0·051	0·102	0·205	0·409
Equiv. conductivity	59·2	42·7	34·2	23·6

The ratios between the various values are :

Normality of HCl	0·051	0·102	0·205	0·409
Ratio of H activity	1·00	1·44	2·21	3·53
Ratio of equiv. conductivity	1·00	0·72	0·63	0·40

As might be expected in this solvent, there was no increase in conductivity when 0·051*N*-acetic acid was added to 0·102*N*-hydrochloric acid.

As hydrogen chloride in 80% acetone showed the properties of a weak electrolyte it follows from the results in Table I that undissociated hydrogen chloride also catalyses the reaction, probably by hydrogen bonding (Rolfe and Hinshelwood, *Trans. Faraday Soc.*, 1934, **30**, 935; Fairclough and Hinshelwood, *J.*, 1939, 593) :

$$X\text{-}C_6H_4\text{-}CH{:}N\text{-}OAc + HCl \rightleftharpoons X\text{-}C_6H_4\text{-}CH{:}N\text{-}\overset{\overset{H}{|}}{O}Ac \cdots Cl$$

The oxime formed in the primary reaction and the hydroxylamine formed in the secondary reaction will compete with the acetyl-aldoxime for the available protons and, if no counter-effect operates, there should be a gradual diminution in the rate constant as the reaction proceeds; as this is not observed the acetic acid produced in the reaction must also act as a catalyst to counteract the above competition effect. The addition of further acetic acid has a pronounced effect on the rate constant, that for 0·1*N*-hydrochloric plus 0·05*N*-acetic acid being about 11% greater than that for 0·1*N*-hydrochloric acid alone.

The rate constants have been measured at two different temperatures, and the approximate activation energy and frequency constant calculated from the Arrhenius equation, the results being given in Table IV.

TABLE IV.

X in X·C_6H_4·CH:N·OAc.	Solvent.	Normality of HCl.	$T°$, K.	$k \times 10^5$, secs.$^{-1}$.	E, cals. per g.-mol.	$\log_{10} H$, sec.$^{-1}$.
m-NO_2	80%	0·409	284·38	2·577	15,100	7·02
	80%	0·409	298·00	8·707		
m-NO_2	98%	0·204	284·38	4·331	15,500	7·57
	98%	0·204	298·00	15·14		
p-OMe	80%	0·409	284·38	2·848	17,000	8·47
	80%	0·409	298·00	11·12		
o-OMe	80%	0·409	284·38	2·780	14,900	6·88
	80%	0·409	298·00	9·200		
p-Me	80%	0·409	284·38	2·193	18,900	9·92
	80%	0·409	298·00	10·11		
o-NO_2	80%	0·409	288·18	2·658	14,900	6·68
	80%	0·409	298·00	6·226		

The side reaction mentioned above has been investigated in so far as it might affect the rate constants of the hydrolysis of the acetyl derivatives in acetone containing low concentrations of water. The formation of mesityl oxide and phorone from acetone under the influence of hydrogen chloride is well known, but little work has been done on the addition of hydrogen chloride to these compounds. Vorlander and Hayakawa (*Ber.*, 1903, **36**, 3536) prepared a compound containing two proportions of hydrogen chloride to one of phorone; they give no structural formula but it is presumably $CO(CH_2{\cdot}CMe_2Cl)_2$. It is stated that with cold water it loses hydrogen chloride very slowly but with warm water more rapidly, and that the loss of hydrogen chloride can be followed by titration with warm baryta solution. Rupe and Kessler (*Ber.*, 1909, **42**, 4715) prepared $Me_2CBr{\cdot}CH_2{\cdot}COMe$ by the action of hydrogen bromide on mesityl oxide cooled in ether–solid carbon dioxide and Thayer and McElvain (*J. Amer. Chem. Soc.*, 1928, **50**, 3353) prepared the corresponding chloro-compound by the action of thionyl chloride on diacetone alcohol. From the descriptions given both these compounds seem moderately stable to cold dilute alkali.

We have found that, in the presence of hydrogen chloride, acetone containing less than 4% of water undergoes a slow reaction which involves the disappearance of protons which can be followed by diluting the reaction mixture with a large excess of ice-cold water and titration with baryta. In the initial period (up to 24 hours at 25°) the rate constant fell progressively but thereafter (up to 40 days) a good first-order constant was obtained. With acetone containing

4% of water this side reaction could only just be detected after 4 days, but the rate constant increases at least until the water content is reduced to 1%.

In view of the possibility of the formation of both mesityl oxide and phorone, and of the addition to the former of one molecule of hydrogen chloride and to the latter of one or two molecules of hydrogen chloride, it is not possible to decide from this kinetic study alone what reaction or combination of reactions the rate constant represents; we were interested in it, however, only as an item to be allowed for in the determination of the rate constants for the hydrolysis of acetyl-aldoximes in acetone containing small amounts of water. From the work of others it seems that the addition of hydrogen chloride is rapid, so it has been assumed that the rate constant measured corresponds at first to mesityl oxide and phorone formation and later to phorone formation.

The rate constants for phorone formation are given in Table V. This rate constant is decreased by the presence of the products of hydrolysis of acetyl-aldoximes as shown in Tables VI and VII owing, probably, to their competition for protons.

TABLE V.

Phorone formation from acetone at 25°.

H_2O, %.	Normality of HCl.	$k \times 10^4$, secs.$^{-1}$.	% Reaction at $t = \infty$, HCl absorbed/HCl taken.
2	0·102	1·13	31·3
2	0·204	1·92	40·6
1	0·102	1·65	57·1
0·5	0·102	1·53	66·6
0·5	0·204	2·19	66·6

TABLE VI.

Phorone formation in 98% acetone at 25° in presence of 0·204N-HCl, 0·044N-acetic acid, and aldoxime.

Oxime X·C_6H_4·CH:N·OH where X is	Molecular concn. of oxime.	$k \times 10^4$, secs.$^{-1}$.
m-NO_2	0·0635	1·125
p-OMe	0·0630	1·124
o-OMe	0·0635	1·130
p-Me	0·0545	1·304

TABLE VII.

Phorone formation in 98% acetone at 25° in presence of products of hydrolysis of acetyl-aldoximes.

Compound hydrolysed, X·C_6H_4·CH:N·OAc where X is	Normality of HCl.	$k \times 10^4$, secs.$^{-1}$.
p-OMe	0·204	1·323
o-OMe	0·204	1·437
p-Me	0·204	1·234
o-NO_2	0·204	1·459
m-NO_2	0·102	1·087
m-NO_2 (99·5% acetone)	0·139	1·338

EXPERIMENTAL.

Preparation of Materials.—The acetyl derivatives of aldoximes were prepared in the usual way from the oxime and acetic anhydride and purified by crystallisation either from acetone and water or from light petroleum.

Rectified acetone (2½ l.) was heated under reflux for 4 hours with potassium permanganate (40 g.) and calcium oxide (40 g.) and then distilled through a column packed with glass helices and fitted with a Whitmore still head. The head and the tail fractions were rejected. Distilled water was boiled in a Pyrex flask, cooled, and kept in an atmosphere free from carbon dioxide. The amount of water in the purified acetone was determined by its refractive index: n_D^{20} = 1·3560, 1·3561, 1·3560, 1·3559; average 1·3560. The average value for the distilled water measured at the same time was n_D^{20} 1·3324. From the graph constructed by plotting % of water against n for acetone–water mixtures from data in International Critical Tables the purified acetone was found to contain 99·7% of acetone.

Method.—A water-bath was used, the temperature being held constant to ±0·01° by a thermostat. The reactions were carried out in stoppered graduated flasks.

A weighed quantity of the acetyl derivative, equivalent to approx. 0·05M-solution in the volume used (usually 100 c.c. in all), was dissolved in slightly less than the final volume of acetone and allowed to reach 25° in the bath. The requisite volumes of aqueous hydrochloric acid and distilled water were then added, the mixture was well shaken, and the volume made up with acetone to the mark. After further shaking the flask was placed in the thermostat; portions (5 c.c.) were withdrawn at suitable intervals, poured into ice-cold CO_2-free distilled water and immediately titrated against standard (approx. 0·05N.) barium hydroxide using phenolphthalein. The barium hydroxide was kept out of contact with carbon dioxide and was standardised twice daily with approx. 0·2N-hydrochloric acid, checked at intervals

against borax. The zero reading was taken 7—10 minutes after mixing and the infinity reading after ten half-times. Pure concentrated hydrochloric acid (10·23N.) was used in making up solutions containing more than 90% of acetone, the same acid diluted five-fold with water was used for making up mixtures containing 80—90% of acetone. For experiments with acetone containing less than 1% of water pure dry hydrogen chloride was passed into a small volume of well-cooled aqueous acetone and the required volume of this added to the main solution.

The following are typical results:

0·0477M-*m*-$NO_2{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}OAc$, 0·102N-HCl; 25·00°. Solvent: 5 vols. of 2N-HCl + 15 vols. of H_2O made up to 100 vols. with acetone.

Titration $= r$.	$\infty - r = (a - x)$.	$1 + \log_{10}(a - x)$.	$t \times 10^{-2}$, secs.	$k \times 10^4$, secs.$^{-1}$.	Titration $= r$.	$\infty - r = (a - x)$.	$1 + \log_{10}(a - x)$.	$t \times 10^{-2}$, secs.	$k \times 10^4$, secs.$^{-1}$.
5·68	1·97	1·2945	0	—	7·12	0·53	0·7243	702	1·871
5·81	1·84	1·2648	36	1·900	7·30	0·35	0·5441	918	1·883
5·95	1·70	1·2304	78	1·893	7·38	0·27	0·4314	1,026	1·937
6·07	1·58	1·1987	117	1·886	7·55	—	—	(45)*	—
6·17	1·48	1·1703	153	1·870	7·58	—	—	(52)*	—
6·25	1·40	1·1461	180	1·899	7·64	—	—	(70)*	—
6·50	1·15	1·0607	279	1·930	7·65 (∞)	—	—	(84)*	—

Average: $k = 1{\cdot}896 \times 10^{-4}$ sec.$^{-1}$. * t (hrs.).

0·0480M-*m*-$NO_2{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}OAc$, 0·205N-HCl; 25·00°. Solvent: 10 vols. of 2N-HCl + 10 vols. of H_2O, made up to 100 vols. with acetone.

8·54	1·71	1·2330	0	—	9·23	1·02	1·0086	1,404	3·681
8·62	1·63	1·2122	12	3·992	9·39	0·86	0·9345	1,800	3·820
8·76	1·49	1·1732	36	3·824	9·90	0·35	0·5441	4,080	3·889
8·89	1·36	1·1335	60	3·819	10·20	0·05	—	(28·5)*	—
9·04	1·21	1·0828	90	3·844	10·25	—	—	(214)*	—

Average: $k = 3{\cdot}838 \times 10^{-4}$ secs.$^{-1}$. * t (hrs.).

0·0950M-*m*-$NO_2{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}OAc$, 0·205N-HCl; 25·00°. Solvent: 5 vols. of 2N-HCl and 5 vols. of H_2O, made up to 50 vols. with acetone.

8·83	3·32	1·5211	0	—	10·39	1·76	1·2455	168	3·759
9·12	3·03	1·4814	24	3·808	11·44	0·71	0·8513	402	3·836
9·38	2·77	1·4425	48	3·772	12·07	—	—	(26·25)*	—
9·68	2·47	1·3927	78	3·792	12·15(∞)	—	—	(214)*	—
10·07	2·08	1·3181	126	3·710					

Average: $k = 3{\cdot}779 \times 10^{-4}$ secs.$^{-1}$. * t (hrs.).

0·0463M-*m*-$NO_2{\cdot}C_6H_4{\cdot}CMe{:}N{\cdot}OAc$, 0·409N-HCl; 25·00°. Solvent: 20 vols. of 2N-HCl, made up to 100 vols. with acetone.

38·70	3·77	1·5763	0	—	41·32	1·15	1·0607	108	11·00
39·17	3·30	1·5185	12	11·09	41·78	0·69	0·8388	154	10·97
39·57	2·90	1·4624	24	10·93	41·92	0·55	0·7404	177	10·88
39·94	2·53	1·4031	36	11·08	42·48 / 42·46	42·47(∞)	—	—	(22)*	—
40·35	2·12	1·3263	54	10·66			—	—	(28)*	—
40·85	1·62	1·2095	78	10·83					

Average: $k = 10{\cdot}93 \times 10^{-4}$ secs.$^{-1}$. * t (hrs.).

The following are examples of the interaction of acetone and hydrochloric acid. In the earlier stages where it is supposed that mesityl oxide and phorone are formed a falling rate constant is obtained but the final stage, where it is supposed that phorone formation only takes place, was isolated by taking t at 756×10^3 secs.

0·102N-HCl; 25·00°. Solvent: 1 vol. of 10N-HCl + 1 vol. of H_2O, made up to 100 vols. with acetone.

Titration $= r$.	$\infty - r = (a - x)$.	$1 + \log_{10}(a - x)$.	$t \times 10^{-2}$, secs.	$k \times 10^4$, secs.$^{-1}$.	$t \times 10^{-2}$, secs.	$k \times 10^4$, secs.$^{-1}$.
10·46	3·18	1·5024	0	—	—	—
10·41	3·13	1·4955	42	3·783	—	—
10·30	3·03	1·4814	180	2·687	—	—
10·08	2·80	1·4472	756	1·682	0	—
9·98	2·70	1·4314	1,044	1·566	288	1·263
9·80	2·52	1·4014	1,728	1·346	972	1·085
9·37	2·09	1·3201	3,384	1·241	2,628	1·114
8·86	1·58	1·987	5,940	1·176	5,184	1·104
8·29	1·01	1·0043	9,576	1·198	8,820	1·156
7·81	0·47	0·6721	17,208	1·111	16,452	1·084
7·42	—	—	(769)*	—	—	—
7·28(∞)	—	—	(1032)*	—	—	—

Average for phorone formation: $k = 1{\cdot}134 \times 10^{-4}$ secs.$^{-1}$. * t (hrs.).

0·204N-HCl; 25·00°. Solvent: 2 vols. of 2N-HCl, made up to 100 vols. with acetone.

Titration = r.	$\infty - r = (a - x)$.	$1 + \log_{10}(a - x)$.	$t \times 10^{-4}$, secs.	$k \times 10^{5}$, secs.$^{-1}$.	$t \times 10^{-4}$, secs.	$k \times 10^{5}$, secs.$^{-1}$.
20·51	8·23	1·9154	0	—	—	—
20·44	8·16	1·9117	27	3·156	—	—
20·38	8·10	1·9055	54	2·943	—	—
20·05	7·77	1·8904	198	2·907	—	—
19·93	7·65	1·8837	261	2·797	—	—
19·13	6·85	1·8357	756	2·428	0	—
18·75	6·47	1·8109	1,044	2·358	288	1·983
17·98	5·70	1·7559	1,656	2·218	900	2·042
15·63	3·35	1·5250	4,356	2·064	3,000	1·986
14·53	2·25	1·3522	16,840	1·896	6,084	1·830
12·86	0·58	0·7634	14,004	1·894	13,248	1·864
12·49	0·21	0·3222	19,980	1·836	19,234	1·812
12·28(∞)	—	—	(1008) *	—	(987) *	—

Average for phorone formation: $k = 1·920 \times 10^{-5}$ secs.$^{-1}$. * t (hrs.).

The following is an example of an experiment where phorone hydrochloride formation was followed after the main reaction was completed, that is, in the presence of the hydrolysis products of the acetyl derivative (Table VII). The conditions were: 0·0478M-*m*-NO_2·C_6H_4·CH:N·OAc; 0·102 N-HCl; 25·00°; solvent: 1 vol. of 10N-HCl + 1 vol. of H_2O, made up to 100 vols. with acetone. The reaction was allowed to proceed for 50 hours to complete hydrolysis and the titration at that point was that for zero time in the side reaction.

Titration = r.	$\infty - r = (a - x)$.	$1 + \log_{10}(a - x)$.	t, hrs.	$k \times 10^{5}$, secs.$^{-1}$.
12·72	2·18	1·3385	0	—
12·36	1·82	1·2601	44	1·140
11·34	0·80	0·9031	269	1·035
10·82	0·28	0·4472	525	1·086
10·54	—	—	1,110	—

Average: $k = 1·087 \times 10^{-5}$ secs.$^{-1}$.

Experiments were also conducted on phorone formation in the presence of added oxime and acetic acid, the hydrolysis products in the first reaction. The following is an example.

0·204N-HCl; added 0·0635M-*m*-NO_2·C_6H_4·CH:N·OH; 0·044M-AcOH; 25·00°. Solvent: 2 vols. of 10N-HCl, made up to 100 vols. with acetone.

Titration = r.	$\infty - r = (a - x)$.	$1 + \log_{10}(a - x)$.	$t \times 10^{-4}$, secs.	$k \times 10^{5}$, secs.$^{-1}$.	$t \times 10^{-4}$, secs.	$k \times 10^{5}$, secs.$^{-1}$.
21·01	6·01	0·7789	0	—	—	—
21·90	5·90	0·7709	81	2·275	—	—
21·84	5·84	0·7664	144	1·999	—	—
21·79	5·79	0·7627	198	1·884	—	—
21·37	5·37	0·7300	870	1·294	0	—
20·82	4·82	0·6830	1,809	1·221	939	1·153
19·64	3·64	0·5611	4,322	1·142	3,522	1·105
18·69	2·69	0·4298	7,020	1·145	6,150	1·124
17·84	1·84	0·2648	10,447	1·133	9,577	1·119
16·00(∞)	—	—	(1,032)*	—	—	—

Average for phorone formation: $k = 1·125 \times 10^{-5}$ secs.$^{-1}$. * t (hrs.).

From a consideration of the change in rate constant, in the experiment quoted above, of the action of hydrochloric acid on acetone leading to mixed mesityl oxide and phorone formation at first and then to phorone formation only, it was assumed that while the hydrolysis was taking place the secondary reaction proceeded at a rate $k = 2(1·087 \times 10^{-5})$ during the first 90×10^{3} secs., $k = 1·5(1·087 \times 10^{-5})$ up to 243×10^{3} secs., and $k = 1·087 \times 10^{-5}$ for from 24 to 50 hours. From this it is possible to calculate the amount of hydrochloric acid removed from the system by mesityl oxide and phorone formation during the hydrolysis in terms of barium hydroxide used for titration. These corrections must be added to the actual titre to follow the kinetics of the hydrolysis. In this case they were:

$t \times 10^{3}$ secs. ...	12	24	42	54	72	90	117	153	198	243	24 hrs.	50 hrs.
Correction, c.c. ...	0·01	0·01	0·02	0·03	0·04	0·06	0·07	0·09	0·10	0·13	0·39	0·62

A run was then performed using the same concentration of acetyl derivative, hydrochloric acid, and water, and these corrections were applied.

0·0478*N*-*m*-$NO_2{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}OAc$; 0·102*N*-HCl. Solvent: 1 vol. of 10*N*-HCl + 1 vol. of H_2O, made up to 100 vols. with acetone.

Actual titration.	Corrected titration = r.	$\infty - r$ = $(a - x)$.	$1 + \log_{10}$ $(a - x)$.	$t \times 10^{-4}$, secs.	$k \times 10^5$, secs.$^{-1}$.
9·40	9·40	3·56	1·5539	0	—
9·68	9·69	3·29	1·5172	12	7·044
9·94	9·95	3·03	1·4814	24	6·956
10·28	10·30	2·68	1·4281	42	6·898
10·46	10·49	2·49	1·3962	54	6·724
10·78	10·82	2·16	1·3345	72	7·018
11·00	11·06	1·92	1·2833	90	6·925
11·34	11·41	1·57	1·1959	117	7·011
11·64	11·73	1·25	1·0969	153	6·878
11·99	12·09	0·89	0·9494	198	7·030
12·18	12·31	0·67	0·8261	243	6·898
12·58	12·97	—	—	(24)*	—
12·36	12·98 ∞	—	—	(50)*	—

Average: $k = 6{\cdot}938 \times 10^{-5}$ secs.$^{-1}$. * t (hrs.).

The attainment of a steady infinity reading is regarded as a justification for the application of the correction.

Another example using a different acetyl derivative gave the following figures.

0·0807*M*-*p*-$MeO{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}OAc$; 0·204*N*-HCl; 25·00°. Solvent: 2 vols. of 10*N*-HCl, made up to 100 vols. with acetone.

Actual titration.	Corrected titration = r.	$\infty - r$ = $(a - x)$.	$1 + \log_{10}$ $(a - x)$.	$t \times 10^{-4}$, secs.	$k \times 10^5$, sec.$^{-1}$.
21·09	21·09	3·85	1·5853	0	—
21·91	21·93	3·01	1·4786	12	20·51
22·56	22·60	2·34	1·3692	24	20·76
23·02	23·08	1·86	1·2695	36	20·22
23·40	23·48	1·46	1·1644	48	20·21
23·69	23·79	1·15	1·0607	60	20·14
24·03	24·16	0·78	0·8921	78	20·47
24·32	24·48	0·46	0·6628	105	20·23
24·64	24·83	—	—	132	—
24·66	24·90	—	—	168	—
24·67	24·94	—	—	204	—
[24·64	24·94(∞)	—	—	252 (?) *	—
[24·64	—	5·94	1·7738	0	—
24·18	—	5·48	1·7388	(18)*	0·1244
23·01	—	4·91	1·6911	(40)*	0·1322
21·75	—	3·05	1·4843	(144)*	0·1286
20·57	—	1·87	1·2718	(240)*	0·1338
19·53	—	0·83	0·9191	(406)*	0·1347
18·70(∞)	—	—	—	(954)*	—

Average for hydrolysis: $k = 20{\cdot}36 \times 10^{-5}$ secs.$^{-1}$. * t (hrs.).
Average for side reaction: $k = 1{\cdot}323 \times 10^{-4}$ secs.$^{-1}$.

Examination of End-products.—The reaction mixture from the acetyl-*m*-nitrobenzaldoxime hydrolysed by 0·4*N*-hydrochloric acid in 80% acetone was poured into excess of aqueous 2*N*-sodium carbonate and extracted several times with ether. The ethereal layers were evaporated in a current of air, dried in a vacuum, and weighed. The product was redissolved in ether and extracted several times with sodium hydrogen sulphite solution to remove aldehyde. The ethereal layer was evaporated at room temperature, and the product dried, weighed, and identified as *a*-*m*-nitrobenzaldoxime. The aqueous layer was treated with excess of sodium carbonate and again extracted with ether, and after evaporation the *m*-nitrobenzaldehyde was recovered and identified. In two experiments, each starting with 1 g. of acetyl derivative, the total yield of product isolated was 92·7% and 90·6% respectively and the yield of oxime recovered was 41·4% and 40·7% respectively.

From oxime instead of the acetyl derivative, hydrolysed under the same conditions, a similar mixture of oxime and aldehyde was recovered.

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253. *The Isomerism of the Oximes. Part XLIII. The Kinetics of the Pyrolysis of Acyl Derivatives.*

By Douglas Ambrose and O. L. Brady.

A kinetic study has been made of the pyrolysis of acyl derivatives of the aldoximes: $X{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}OR = X{\cdot}C_6H_4{\cdot}CN + HOR$.

The reaction shows first-order kinetics, and the rate constants are in the order X = *o*-MeO > *p*-Me_2N > *p*-MeO > 3 : 4-CH_2O_2 > H > *m*-MeO > *o*-NO_2 > *m*-NO_2 = *p*-NO_2; R = $Cl_3C{\cdot}CO$ > $Ph_2N{\cdot}CO$ > EtO·CO > *p*-$NO_2{\cdot}C_6H_4{\cdot}CO$ > PhCO > *p*-MeO·$C_6H_4{\cdot}CO$ = $CH_2Cl{\cdot}CO$ > Ac.

The mechanism of the reaction is discussed and it is suggested that the pyrolysis can best be represented as involving electron shifts, without separation of charges, in a structure of the acyl compound in which hydrogen bonding is present.

The formation of nitriles by the pyrolysis of acyl derivatives of aldoximes has been known for some time; for example, Neber, Hartung, and Ruopp (*Ber.*, 1925, **58**, 1239) found that benzoyl-α-*p*-nitrobenzaldoxime, heated for 30 minutes at 140°, gave benzoic acid and a quantitative yield of *p*-nitrobenzonitrile, $NO_2{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}OBz \longrightarrow BzOH + NO_2{\cdot}C_6H_4{\cdot}CN$, and similar results were obtained with other acyl derivatives by Lindemann and Thiele (*Annalen*, 1926, **449**, 74), von Auwers and Krese (*ibid.*, **450**, 283), and Lindemann, Könitzer, and Romanoff (*ibid.*, 1927, **456**, 284). In addition, one of us has observed that the carefully purified acetyl derivatives of some substituted α-benzaldoximes, prepared in the course of other investigations, when kept in tightly corked tubes in the dark for several years, decomposed and acquired an odour of acetic acid and nitrile. This was noticed in the case of the acetyl derivatives of α-*p*-methoxy-, α-3 : 4-dimethoxy-, and α-3 : 4-methylenedioxy-benzaldoximes, but the acetyl derivatives of α-*m*- and α-*p*-nitrobenzaldoximes under similar conditions remained practically unchanged. This suggested that the electron-demand or -release of the substituted benzene nucleus had considerable influence on the rate of decomposition.

A kinetic study has now been made of this pyrolysis at various temperatures in xylene and in the absence of solvents.

The reaction shows first-order kinetics, and the general result of varying the substituent X in the nucleus in compounds of the general formula $X{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}OR$ indicates a decrease in the rate constant in the order *o*-MeO > *p*-Me_2N > *p*-MeO > 3 : 4-CH_2O_2 > H > *m*-MeO > *o*-NO_2 > *m*-NO_2 = *p*-NO_2 (Tables I—IV).

Variations in R produce a decrease in rate constant in the order $Cl_3C{\cdot}CO$ * > $Ph_2N{\cdot}CO$ > EtO·CO > *p*-$NO_2{\cdot}C_6H_4{\cdot}CO$ > Bz > *p*-MeO·$C_6H_4{\cdot}CO$ = $CH_2Cl{\cdot}CO$ > Ac (Table V).

The possible mechanisms of the decomposition may be represented:

$$X{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}OR \rightleftharpoons \begin{cases} X{\cdot}C_6H_4{\cdot}\overset{\oplus}{C}{:}N{\cdot}OR + \overset{\ominus}{H} \\ X{\cdot}C_6H_4{\cdot}CH{:}\overset{\oplus}{N} + \overset{\ominus}{O}R \end{cases} \longrightarrow X{\cdot}C_6H_4{\cdot}C{\equiv}N + HOR \quad \begin{matrix} (1) \\ (2) \end{matrix}$$

$$X{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}OR \rightleftharpoons \begin{cases} X{\cdot}C_6H_4{\cdot}\overset{\oplus}{C}{:}N{\cdot}OR + \overset{\ominus}{H} \\ X{\cdot}C_6H_4{\cdot}CH{:}\overset{\oplus}{N} + \overset{\ominus}{O}R \end{cases} \longrightarrow X{\cdot}C_6H_4{\cdot}\overset{+}{C}{:}\overset{-}{N} + HOR \quad \begin{matrix} (3A) \\ (3B) \end{matrix}$$

$$X{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}OR \rightleftharpoons X{\cdot}C_6H_4{\cdot}\dot{C}{:}N{\cdot}OR + \dot{H}$$

$$X{\cdot}C_6H_4{\cdot}\dot{C}{:}N{\cdot}OR \longrightarrow X{\cdot}C_6H_4{\cdot}C{\equiv}N + \dot{O}R$$

$$\dot{H} + \dot{O}R \longrightarrow HOR \quad (4A)$$

$$X{\cdot}C_6H_4{\cdot}CH{:}NOR \rightleftharpoons X{\cdot}C_6H_4{\cdot}CH{:}\dot{N} + \dot{O}R$$

$$X{\cdot}C_6H_4{\cdot}CH{:}\dot{N} \longrightarrow X{\cdot}C_6H_4{\cdot}C{\equiv}N + \dot{H}$$

$$\dot{H} + \dot{O}R \longrightarrow HOR \quad (4B)$$

Mechanisms (1), (2), (3A), and (3B) represent heterolytic fissions, and (4A) and (4B) homolytic fissions. (4A) and (4B) might occur simultaneously, as suggested for the

* From qualitative observations only.

decomposition of the diazoacetates in non-ionising solvents (Grieve and Hey, *J.*, 1934, 1797):

$$R{\cdot}N{:}N{\cdot}OAc \longrightarrow \dot{R} + N{\equiv}N + \dot{O}Ac$$

$$CHPh{:}N{\cdot}OAc \longrightarrow \dot{H} + Ph{\cdot}C{\equiv}N + \dot{O}Ac \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4C)$$

or might give rise to chain reactions:

$$X{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}OR \longrightarrow X{\cdot}C_6H_4{\cdot}C\dot{H}{:}N{\cdot}OR$$

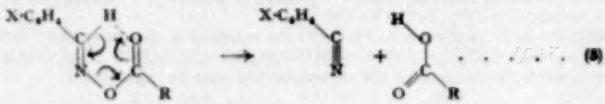
$$X{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}OR + \dot{O}R \longrightarrow X{\cdot}C_6H_4{\cdot}\dot{C}{\cdot}N{\cdot}OR + HOR$$

$$X{\cdot}C_6H_4{\cdot}\dot{C}{:}N{\cdot}OR \longrightarrow X{\cdot}C_6H_4{\cdot}C{\equiv}N + \dot{O}R \quad . \quad . \quad . \quad . \quad . \quad . \quad (4D)$$

Mechanism (1) is ruled out because electron-recession due to X from the methine-carbon atom would favour the reaction, and electron-accession retard it, whereas the opposite is the case. Neither (3A) nor (3B) leading to the other canonical form of the nitrile would be favoured by increasing the electron-attracting nature of R and such fissions seem unlikely.

On the other hand, the observed effects of electronic displacements on the rate constants support mechanism (2), but there are objections to its adoption in so simple a form. First, it involves an ionisation with the consequent large energy barrier to be overcome; this might be accomplished if there was solvation of ions but this is not likely to occur to any extent in xylene; moreover, there was no marked increase in the rate of reaction in benzonitrile; further in the case of the carbethoxy-derivatives the rate constant was generally higher in the absence of solvent (Table IV). Secondly, the effects due to variation in X and R are small compared with those observed in the hydrolysis of substituted carboxylic esters; for example, the rate constant for the pyrolysis of carbethoxy-*p*-methoxybenzaldoxime is about 3·6 times greater than that of carbethoxy-*p*-nitrobenzaldoxime, and that of *p*-nitrobenzoyl-*p*-methoxybenzaldoxime only about 1·6 times greater than that of *p*-methoxybenzoyl-*p*-methoxybenzaldoxime, whereas that for the hydrolysis of ethyl *p*-nitrobenzoate is at least 500 times greater than that of ethyl *p*-methoxybenzoate (Ingold and Nathan, *J.*, 1936, 222; Evans, Gordon, and Watson, *J.*, 1937, 1430; 1938, 1439).

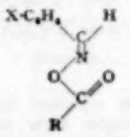
If, however, hydrogen bonding exists in the acyl derivatives of α-aldoximes as suggested by Benger and Brady (*J.*, 1950, 1221) the pyrolysis can be represented as involving electron shifts without separation of charges:



(5)

This mechanism is free from the objections to (2) indicated above; no ionisation is involved, electron-release from $X{\cdot}C_6H_4{-}$ would favour the rupture of the N–O bond but hinder the rupture of the C–H bond, and the effect of passing from X = *p*-MeO to X = *p*-NO_2 would be less than in the hydrolysis of the ethyl benzoates since the pyrolysis is conditioned by two factors influenced in opposite senses by the substituent group. Electron-withdrawal by R, whilst it would retard the electron shift from the doubly-bound oxygen atom, would favour it from the nitrogen–oxygen bond which is probably the determining factor in the reaction. In this connection one may note the extreme instability of the trichloroacetyl derivatives, even trichloroacetyl-α-*p*-nitrobenzaldoxime decomposing when kept at room temperature for a few hours (Benger and Brady, *loc. cit.*).

Further information would be afforded on the validity of the hypothesis in reaction (5) by the study of the pyrolysis of acetyl-β-aldoximes where hydrogen bonding would not readily occur:



Unfortunately the acetyl-β-aldoximes are sensitive to traces of acids, being isomerised rapidly thereby to the α-compounds; so, since acetic acid is one of the products of the

decomposition, they cannot be used. Possibly the carbethoxy-compounds would be free from this objection as the ethyl hydrogen carbonate first formed decomposes to carbon dioxide and ethanol: $R{\cdot}CH{:}NO{\cdot}CO_2Et \longrightarrow RCN + HO{\cdot}CO_2Et \longrightarrow CO_2 + HOEt$; but, so far, it has not been found possible to prepare carbethoxy-β-aldoximes.

A qualitative investigation has been made of the pyrolysis of carbanilino-α- and -β-aldoximes (Sharawy, unpublished), but the reaction is complicated by the phenylcarbamic acid first formed decomposing in two ways, to give aniline and diphenylurea, and it has not been possible yet to work out a reliable analytical technique for following the reaction kinetically:

$$R{\cdot}CH{:}NO{\cdot}CO{\cdot}NHPh \longrightarrow RCN + HO{\cdot}CO{\cdot}NHPh$$
$$HO{\cdot}CO{\cdot}NHPh \longrightarrow CO_2 + PhNH_2$$
$$2HO{\cdot}CO{\cdot}NHPh \longrightarrow CO_2 + H_2O + CO(NHPh)_2$$

In addition carbanilino-β-benzaldoxime gave some benzaldehyde, indicating a different mode of decomposition.

Many pyrolyses are now regarded as taking place by homolytic fission, and mechanisms (4A), (B4), (4C), and (4D) cannot be excluded.

The effect of electron-accession or *vice versa* on the rate constant of homolytic fission reactions does not seem to be established. It has been suggested by Grieve and Hey (*loc. cit.*) and Waring and Abrams (*J. Amer. Chem. Soc.*, 1941, **63**, 2757) that the decomposition of the diazoacetates in non-ionising solvents involves homolytic fission. Now the rate constant for the decomposition of $X{\cdot}C_6H_4{\cdot}N{:}N{\cdot}OR$ is practically uninfluenced by the nature of X but is markedly influenced by the nature of R in the order $HCO < MeCO < EtCO < n\text{-}C_3H_7CO$ (Hey and Waters, *J.*, 1948, 882), but in the decomposition of compounds of the type $p\text{-}X{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}O{\cdot}CO{\cdot}C_6H_4Y\text{-}p$ the ratio $k(X = MeO)/k(X = NO_2)$ is as much as 3·5 : 1, whilst $k(Y = NO_2)/k(Y = MeO)$ is only 1·0 : 1.

The absence of by-products in the reaction is rather against homolytic fission; the formation of the very sparingly soluble *p*-nitrobenzylideneazine, $NO_2{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}N{:}CH{\cdot}C_6H_4{\cdot}NO_2$, which might be formed by the pairing of $NO_2{\cdot}C_6H_4{\cdot}CH{:}N$ radicals in (4B) could not have escaped notice but small quantities of other by-products might have done so.

Copper has a pronounced catalytic effect on the decomposition (cf. Waters, *J.*, 1942, 266), and the effect of this and other catalysts is being further investigated. On the other hand mercury is not attacked during the pyrolysis, nor are copper salts formed in the presence of calcium carbonate as is observed when free acyl radicals are produced (Waters, *J.*, 1937, 113; Hey and Waters, *J.*, 1948, 882).

The rate constants bring out certain interesting points. It will be seen from Tables II and IV that *m*-MeO retards decomposition as compared with H, whilst *p*-MeO accelerates it; this is in the order of dissociation constants of the acids $X{\cdot}C_6H_4{\cdot}CO_2H$ where *m*-MeO > H > *p*-MeO.

Although the dissociation constant of the *o*-acid is little lower than that of *p*-methoxybenzoic acid the velocity of decomposition of *o*-methoxy-compounds is considerably greater than that of the corresponding *p*-methoxy-derivatives.

Tables I and II indicate that the rate constants for *o*-nitro-compounds are appreciably higher than for the corresponding *m*- and *p*-nitro-derivatives although the dissociation constant of *o*-nitrobenzoic acid is some 20 times that of *m*- or *p*-nitrobenzoic acid. These results suggested that the possibility of hydrogen bonding between the methine-hydrogen atom and an atom of the *o*-substituent favours the rupture of the C–H bond:

just as in the case of α-*o*-nitrobenzaldoxime it favours attack on the methine-hydrogen atom by OH (Benger and Brady, *loc. cit.*).

The *m*-nitro-compounds apparently decompose somewhat more slowly than the corresponding *p*-nitro-compounds, but it is doubtful if our results are sufficiently accurate to place these compounds in their correct order, and the ratio of the dissociation constants of the corresponding benzoic acids is only 1 : 1·17, so that further speculation on these results is uncalled for.

TABLE I.

Rates of pyrolysis of X·C_6H_4·CH:N·OAc *in xylene*; $k \times 10^5$ *sec.*$^{-1}$.

X.	139°.	120°.	115°.
m-NO_2	8·4	—	0·86
p-NO_2	9·2	—	—
o-NO_2	12·1	—	—
3 : 4-CH_2O_2	19·2	—	1·57
p-MeO	26·5	—	1·95
p-Me_2N	69	4·4	2·92

TABLE II.

Rates of pyrolysis of X·C_6H_4·CH:N·OBz *in xylene*; $k \times 10^5$ *sec.*$^{-1}$.

X.	139°.	130°.	120°.	115°
m-NO_2	31·0	8·8	3·4	—
p-NO_2	—	8·8	—	—
o-NO_2	—	13·0	—	—
m-MeO	—	—	9·2	5·4
H	100	—	11·5	5·6
p-MeO	too fast to measure.	—	16·1	11·1
o-MeO		—	30·7	17·6

TABLE III.

Rates of pyrolysis of X·C_6H_4·CH:N·O·CO·CH_2Cl *in xylene at* 139°.

X.	*m*-NO_2.	*p*-NO_2.	*o*-NO_2.	3 : 4-CH_2O_2.
$k \times 10^5$, sec.$^{-1}$	27·0	32·5	32·5	92·0

TABLE IV.

Rates of pyrolysis of X·C_6H_4·CH:N·O·CO_2Et *at* 118·6°; $k \times 10^5$ sec.$^{-1}$.

X.	In xylene.	Fused, no solvent.
m-NO_2	16·1	—
p-NO_2	17·0	17·7
o-NO_2	27·1	45·9
m-MeO	46·2	50·9
H	50·6	51·0
p-MeO	61·1	73·6
p-Me_2N	112	156
o-MeO	183	336

TABLE V.

Rates of pyrolysis of X·C_6H_4·CH:N·OY; $k \times 10^5$ sec.$^{-1}$.

	X = *p*-MeO.			X = *m*-NO_2.		X = H.
Y.	139°.	120°.	115°.	139°.	118·6°.	118·6°.
Ph_2N·CO	—	—	—	—	36·7	106
EtO·CO	—	61·1 (118·6°)	—	—	16·1	—
p-$NO_2C_6H_4$·CO	—	22·4	—	—	—	—
Bz	too fast	16·1	11·1	31·0	3·4 (120°)	—
p-MeO·C_6H_4·CO	—	12·4.	—	—	—	—
CH_2Cl·CO	115	—	—	27·0	—	—
Ac	26·5	—	1·95	8·4	0·86 (115°)	—

EXPERIMENTAL.

Preparation of Materials.—The acyl derivatives of the aldoximes were prepared by known methods and recrystallised until the m. p.s corresponded to those in the literature or until a constant m. p. was obtained after 2 successive crystallisations. The thermometer was checked with a standard. A number of discrepancies were observed, *viz.*:

Chloroacetyl-α-*p*-nitrobenzaldoxime, m. p. 128°, chloracetyl-α-*p*-methoxybenzaldoxime, m. p. 72°; Benger and Brady (*loc. cit.*) found 131° and 60° respectively. Benzoyl-α-*m*-nitrobenzaldoxime, m. p. 175°; Brady and McHugh (*J.*, 1925, **127**, 2414) found 161°.

The carbethoxy-derivatives had m. p.s: *m*-NO_2 95° (97°), *p*-NO_2 108° (109°), *o*-NO_2 42° (42°); *o*-MeO 50°, (52°); H 36—37° (34—35°); *p*-MeO 73° (74°); *p*-Me_2N 116° (118°). The figures in parentheses are those given by Brady and Dunn (*J.*, 1916, **109**, 650), or Brady and McHugh (*J.*, 1923, **123**, 1190).

Carbethoxy-α-m-methoxybenzaldoxime crystallised from light petroleum in colourless needles, m. p. 43° (Found: C, 59·5; H, 5·8; N, 6·4. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·8; N, 6·3%); *p*-methoxybenzoyl-α-*p*-methoxybenzaldoxime had m. p. 149° and *p*-nitrobenzoyl-α-*p*-methoxybenzaldoxime, m. p. 153° both crystallised from benzene.

Commercial xylene was dried over sodium and distilled, the middle 80% being collected.

Kinetic Measurements by Determination of Acid.—Acetyl derivatives. A weighed sample (1—2·5 g.) of the acetyl compound and 25 c.c. of xylene were placed in a round-bottomed flask with ground-glass joint and reflux condenser, and the mixture was rapidly heated to boiling. At suitable intervals the flask was cooled for 15 minutes to avoid loss of acetic acid when breaking the seal between flask and condenser, and a sample withdrawn by a pipette. No allowance was made for the periods of cooling and re-heating, but as far as possible the times of such operations were kept constant. This somewhat crude technique adopted in the earlier experiments was not refined, as the accuracy with which the acetic acid could be determined did not seem to justify it. The withdrawn sample was weighed, water added (15—20 c.c.), and the acid titrated with N/30-barium hydroxide using phenolphthalein. Considerable difficulty was experienced in observing the end point in the titration; unless water was added first, an emulsion of water in xylene was formed and no end point could be obtained; if too much

water was added the end point became indistinct and transitory; attempts to extract the acid before titration did not improve the accuracy. As examples of the results four separate determinations with acetyl-α-*m*-nitrobenzaldoxime gave $k \times 10^3$ varying from 6·9 to 8·8 sec.$^{-1}$ (mean 8·4), with acetyl-α-3 : 4-methylenedioxybenzaldoxime 16·5—22·2 (mean 19·2) and with acetyl-α-*p*-methoxybenzaldoxime 23·0—28·4 (mean 26·5). Even if the extreme values were taken the order of the compounds was not altered.

Later experiments were carried out at 120° and 115° (thermostat) by the method described for the benzoyl derivatives. In these circumstances more concordant results were obtained.

Chloroacetyl derivatives. In these cases the technique was improved by using a small reaction flask (50 c.c.) with a long neck wrapped with compo tubing through which water was passed to act as a condenser. A narrow U-tube through which water was circulated was inserted down the neck, leaving room for the entrance of a pipette to remove samples without interrupting the heating. The higher b. p. of chloroacetic acid (185°) reduced chances of loss in these experiments. The solution was heated to boiling as rapidly as possible and timing started from the beginning of boiling. Samples were withdrawn at intervals into weighed flasks containing about 10 c.c. of water to cool the sample and stop the reaction: the flask was reweighed and its contents titrated. In these circumstances the results of independent determinations of k varied by from 3 to 7%, but we would not claim a reproducibility within 10%.

Benzoyl and substituted benzoyl derivatives. The experiments at the b. p. of xylene were carried out by the same method as for the chloroacetyl derivatives. The experiments at lower temperatures were carried out in a conical flask (100 c.c.) fitted with a cold-finger condenser immersed in an oil-bath controlled to ±0·1° (thermostat). The flask and solution were immersed in the thermostat for 10—15 minutes to reach the correct temperature. A sample (4 c.c.) was then withdrawn into a dry weighed flask cooled in ice, the flask was reweighed, 10—15 c.c. of water were added, and the acid was titrated. This titre was used to calculate the concentration at t_0, and further samples were withdrawn and titrated at intervals. The end points were much sharper in these cases. The results of separate determinations of k agreed to within about 10%. The following are details of one experiment, k being calculated from the equation $k = 2{\cdot}3[\log(1 - a_0) - \log(1 - a)]/(t - t_0)$:

0·805 *G. of benzoyl-α-o-methoxybenzaldoxime in* 21·26 *g. of xylene at* 120°.

t, secs.	Sample removed, g.	Titre, c.c. of 0·0201*N*-$Ba(OH)_2$.	a.	$\log(1 - a)$.	$\log(1 - a_0) - \log(1 - a)$.	$k \times 10^3$, secs.$^{-1}$.
0	3·15	2·30	0·103	−0·047	—	—
600	3·06	5·43	0·249	−0·127	0·077	29·5
1200	3·14	8·51	0·381	−0·205	0·161	30·8
1800	3·13	10·88	0·488	−0·291	0·244	31·2
2400	3·10	12·93	0·586	−0·383	0·336	32·2
3000	3·18	15·05	0·665	−0·475	0·4128	32·8
3600	2·81	14·43	0·722	−0·556	0·509	32·6

Mean value: $k = 31{\cdot}4 \times 10^{-3}$ secs.$^{-1}$.

Effect of metals. The accelerating effect of copper was discovered when a copper, instead of a platinum, stirring-wire was used. Three experiments using acetyl-α-*m*-nitrobenzaldoxime (0·5 g.) in xylene in the presence of 0·005, 0·006, and 0·11 g. of finely divided copper (copper bronze) at 115° gave rate constants from 50 to 500 times those in the absence of copper, but in the limited number of experiments performed no correlation was observed between the rates and the amount of copper added. An experiment with benzoyl-α-benzaldoxime (0·5 g.) in the presence of 0·005 g. of copper at 120° and another at 115° showed rate constants approximately 100 times those without copper.

Mixtures of acetyl-α-3 : 4-methylenedioxybenzaldoxime, acetyl-α-*p*-dimethylaminobenzaldoxime, and finely divided copper, on heating for a few minutes to between 90° and 100°, decompose violently.

Mixtures of acetyl derivatives with finely divided silver, heated for some hours to 100°, or acetyl derivatives, heated in the presence of mercury, gave no indication of attack on the metal. Acetyl derivatives, boiled in xylene in the presence of calcium carbonate and copper, gave no evidence of the formation of copper salts.

Kinetic Measurements from the Evolution of Carbon Dioxide.—The carbethoxy- and diphenylcarbamyl-compounds decompose with the formation of unstable acids which break down to give carbon dioxide and alcohol or diphenylamine:

$$R{\cdot}CH{:}NO{\cdot}CO_2Et \longrightarrow RCN + HO{\cdot}CO_2Et \longrightarrow CO_2 + EtOH$$

$$R{\cdot}CH{:}NO{\cdot}CO{\cdot}NPh_2 \longrightarrow RCN + HO{\cdot}CO{\cdot}NPh_2 \longrightarrow CO_2 + HNPh_2$$

Measurement of this carbon dioxide was used as a means of determining the rate constant. The apparatus was a closed system consisting of a small flask surmounted by a condenser the upper end of which was connected *via* a rubber tube and tap manifold with a gas burette. This burette was jacketed, kept at a temperature constant to about ±½°, and provided with a suitable levelling device. The neck of the flask was surrounded by a vacuum jacket to maintain the temperature gradients constant where it emerged from the thermostat; the flask and condenser assembly was supported in a shaker, so that the mixture was constantly agitated.

The solvent xylene was freshly distilled into the flask for each experiment in a current of dry carbon dioxide to ensure its presaturation; when the flask had warmed to the temperature of the experiment enough carbon dioxide was evolved to fill the apparatus and displace the air initially present. A series of three reaction flasks of varying size (20, 30, and 90 c.c.) was used as it was found desirable to have as

little dead space as possible, and the concentration of reactant was varied by using different amounts of solvent. The experiments were carried out by immersing the flask containing the solvent in the bath and allowing thermal equilibrium to be reached, as indicated by a steady burette reading when the flask was agitated. The seal between condenser and flask was momentarily broken for the insertion of the previously weighed sample in an open capsule, and the apparatus resealed with Faraday wax and fixed in the shaker. The burette had previously been set to zero, and readings of time and volume were then taken throughout the reaction.

In spite of the agitation the evolution of gas was still somewhat irregular and the final volume uncertain, so an adaptation of Guggenheim's method (*Phil. Mag.*, 1926, **2**, 538) was used to determine the rate constants. Readings were taken for approximately 6 times the half period of the reaction and from these a smoothed time–volume curve was drawn from which sets of readings B_1, B_2, . . . and B_1', B_2' . . . at times t_1, t_2, . . . and $t_1' = t_1 + T$, $t_2' = t_2 + T$ . . . respectively, could be obtained. The initial period immediately after the sample had been introduced, when steady conditions had not been reached and the rate of evolution of gas had not reached a maximum, was ignored; this generally covered the first 20% of the reaction. The value of the rate constant was then obtained from the equation, $2{\cdot}3 \log (B_t' - B_t) = kt +$ constant by plotting the values of $\log (B_t' - B_t)$ against t and measuring the slope of the straight line so obtained.

Details for one experiment are given below; variations between the values of the rate constant obtained from different experiments were not more than 10%.

0·340 G. of carbethoxy-α-m-nitrobenzaldoxime in 28·0 g. of xylene at 113·8°.

Time (mins.)	0	10	15	20	25	30	35	40	45	50	55
Burette reading (c.c.)...	0	1·9	2·8	3·8	4·7	5·5	6·2	6·8	7·6	8·4	9·2
Time (mins.)	60	65	70	75	80	85	90	95	100	105	
Burette reading (c.c.)...	9·9	10·6	11·3	11·9	12·6	13·2	13·8	14·4	15·0	15·5	
Time (mins.)	110	115	120	125	130	135	140	145	150	155	
Burette reading (c.c.)...	16·0	16·3	17·0	17·5	18·0	18·4	18·9	19·3	19·7	20·1	
Time (mins.)	160	165	170	175	180	185	190	195	200	205	
Burette reading (c.c.)...	20·5	20·9	21·3	21·7	21·9	22·4	22·6	23·0	23·3	23·4	
Time (mins.)	210	215	220	225	230	235	240	250	260	270	
Burette reading (c.c.)...	23·8	24·1	24·4	24·7	24·9	25·2	25·5	26·0	26·5	26·9	
Time (mins.)	280	290	300	310	320	330	340	350	360	370	
Burette reading (c.c.)...	27·3	27·5	27·9	28·3	28·6	28·8	29·0	29·2	29·5	29·3	
Time (mins.)	380	390	400	410	420	430	440	450	460	470	
Burette reading (c.c.)...	29·7	29·9	30·1	30·3	—	30·6	30·7	30·9	31·0	31·1	
Time (mins.)	480	490	500	510	525	540	555	570	585	600	
Burette reading (c.c.)...	31·3	31·3	31·4	31·4	31·4	31·5	31·6	31·7	31·8	31·7	

From the smoothed graph of the points given above the following values of B and B' were obtained, and hence $\log (B' - B)$:

t.	B.	t'.	B'.	$B' - B$.	$\log (B' - B)$.	t.	B.	t'.	B'.	$B' - B$.	$\log (B' - B)$.
15	2·8	315	28·4	25·6	1·408	165	20·9	465	31·1	10·2	1·009
30	5·4	330	28·8	23·4	1·369	180	22·0	480	31·2	9·2	0·964
45	7·7	345	29·2	21·5	1·332	195	23·0	495	31·3	8·3	0·919
60	9·8	360	29·4	19·6	1·292	210	23·9	510	31·4	7·5	0·875
75	11·9	375	29·7	17·8	1·250	225	24·7	525	31·5	6·8	0·833
90	13·8	390	30·0	16·2	1·210	240	25·5	540	31·6	6·1	0·785
105	15·6	405	30·2	14·6	1·161	255	26·3	555	31·6	5·3	0·724
120	17·0	420	30·4	13·4	1·127	270	26·9	570	31·7	4·8	0·681
135	18·6	435	30·6	12·0	1·079	285	27·4	585	31·8	4·4	0·644
150	19·7	450	30·9	11·2	1·049	300	28·0	600	31·9	3·8	0·580

Hence $k = 10{\cdot}3 \times 10^{-4}$ secs.$^{-1}$.

Subsidiary tests were made to determine the rate at which carbon dioxide is evolved from its supersaturated solution in xylene and these indicated that the rate is several hundred times that of the fastest reaction studied and would not therefore have any effect on the measurements. Besides the carbon dioxide there are also present in the apparatus xylene vapour and the alcohol formed in the reaction. As a result, from the condenser onwards the evolved gas is saturated with xylene and alcohol at the condenser temperature; this does not affect the calculation of the rate constant and may be allowed for in calculating the total volume of gas evolved. Agreement between the measured and calculated volumes of gas was not good, discrepancies amounting to as much as 20%; these may be due to dissolution of carbon dioxide in droplets of liquid formed on the walls of the condenser.

The decomposition of the fused compounds in the absence of solvent was carried out in a reaction flask consisting of a small bulb blown on the end of a B7 socket (Quickfit and Quartz) with an air-condenser consisting of a 7-inch length of 1-mm. capillary tubing on a B7 cone and connected to the gas-burette by rubber tubing. In these experiments a longer period elapsed before thermal equilibrium and the maximum rate of gas evolution were reached, because the flask and sample had to warm up from room temperature; with carbethoxy-*p*-dimethylaminobenzaldoxime (m. p. 116°) at 108° this period was 20 minutes, clearly because until then the material was not completely liquid; with the *p*-nitro-compound at 113·8° there was a sharp break in the plot of $\log (B' - B)$ against t caused by the eventual solidification of the material on formation of *p*-nitrobenzonitrile (m. p. 149°).

In conclusion we thank Mr. E. A. W. Hebdon for valuable help in connection with the apparatus for determining the carbon dioxide evolution, Mrs. B. A. Ambrose for the preparation of some of the compounds used, and the Central Research Fund of the University of London for a grant.

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254. *Lanosterol. Part IX. Ketodihydrolanosterol.*

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The main product of the oxidation of dihydroagnosteryl acetate with perbenzoic acid is the αβ-unsaturated ketone, ketodihydrolanosteryl acetate. Dihydrolanosteryl acetate, on oxidation with chromic acid under mild conditions, gave the same ketone, together with dihydroagnosteryl acetate. Ketodihydrolanosteryl acetate was oxidized by selenium dioxide to a more highly unsaturated ketodidehydrodihydrolanosteryl acetate.

IN a previous communication (*J.*, 1949, 2038), it was reported that titration of dihydroagnosteryl acetate with perbenzoic acid showed an absorption of 1·2 atoms of oxygen per molecule. The oily oxidation product has now been isolated as a solid by treatment with boiling methanol; this, after two further crystallizations, had physical constants closely resembling those reported by Ruzicka *et al.* (*Helv. Chim. Acta*, 1944, **27**, 472) for ketodihydrolanosteryl acetate, obtained by the oxidation of dihydrolanosteryl acetate with ozone.

	M. p.	$[\alpha]_D^{18}$.	$\lambda_{max.}$	log ε.
Ketodihydrolanosteryl acetate	151·5—152·5°	+21·3°	255 mμ.	4·08 (in alcohol)
Perbenzoic acid oxidation product ...	151—152°	+26·0°	252—256 mμ.	4·1 (in chloroform)

Recrystallization of the oxidation product led to a gradual rise in the melting point, indicating that the product was not homogeneous. By chromatography it was resolved into two components, the main fraction, m. p. 151—152°, $[\alpha]_D^{18}$ +24°, gave analytical figures in agreement with the formula $C_{33}H_{52}O_3$ and showed high-intensity absorption in the ultra-violet; the second and minor component, m. p. 184°, also had the formula $C_{33}H_{52}O_3$, but showed no high-intensity ultra-violet absorption.

The major component gave no melting-point depression with ketodihydrolanosteryl acetate prepared according to Ruzicka *et al.* (*loc. cit.*), and the close agreement in the physical constants supports the conclusion that the two substances are identical.

The mother liquors from the perbenzoic acid oxidation of dihydroagnosteryl acetate, after treatment with methanol, gave an uncrystallizable oil, which on treatment with glacial acetic acid and sulphuric acid yielded a colourless crystalline solid, m. p. 205°, $[\alpha]_D^{18}$ +96·3°, transparent to ultra-violet light. Analysis gave figures in agreement with the formula $C_{33}H_{52}O_4$, which indicated that further oxidation of the primary oxidation product probably takes place, but, as would be expected with an αβ-unsaturated ketone, at a much slower rate (cf. Spring and Vickerstaff, *J.*, 1937, 249; Ruzicka *et al.*, *Helv. Chim. Acta*, 1932, **15**, 482, 1285).

It has previously been reported by Marker, Wittle, and Mixon (*J. Amer. Chem. Soc.*, 1937, **59**, 1368) that oxidation of dihydrolanosteryl acetate with chromic acid under mild conditions gave rise to two isomeric ketodihydrolanosteryl acetates. The α-isomer was isolated from the less soluble fraction on crystallization from glacial acetic acid; further crystallization gave a product having m. p. 150°, which was reported to be unaffected by boiling acetic anhydride, and to distil unchanged at 200° in a vacuum, the yield of pure substance being 6—7%. The mother liquors gave the β-isomer, m. p. 152°; this compound gave a 10° depression in melting point when mixed with the α-isomer. Both α- and β-ketodihydrolanosteryl acetate were reported to form the same ketodihydrolanosterol, m. p. 134—135°, on hydrolysis, and this on acetylation gave only β-ketodihydrolanosteryl acetate.

Unfortunately, the only constant available for these compounds is the melting point, which is insufficient in itself to allow comparison with the ketodihydrolanosteryl acetate obtained in our experiments with perbenzoic acid.

Ruzicka *et al.* (*Helv. Chim. Acta*, 1944, **27**, 472) have obtained only one ketodihydrolanosteryl acetate, m. p. 151·5—152·5°, $[\alpha]_D$ +18·2°, in the chromic acid oxidation of dihydrolanosteryl acetate, although the reaction conditions were somewhat different from those described by Marker and his co-workers.

Numerous unsuccessful attempts have been made by us to repeat the preparation of

α-ketodihydrolanosteryl acetate following the directions of Marker *et al.* (*loc. cit.*), although no difficulty was experienced in the isolation of the β-ketodihydrolanosteryl acetate.

The less soluble fraction of crude material from the chromic acid oxidation of dihydrolanosteryl acetate was obtained in yields varying from less than 1% to 14%, under apparently the same reaction conditions. Exhaustive purification of this fraction, either according to Marker or by repeated chromatography, yielded a substance, m. p. 149—150°, $[\alpha]_D^{18}$ +80·0°, an admixture of which with β-ketodihydrolanosteryl acetate had m. p. 139—141°. Analysis of this compound showed that it was in fact impure dihydroagnosteryl acetate ($[\alpha]_D^{20}$ +87·8°). The ultra-violet absorption spectrum ($\lambda_{max.}$ = 242 mμ.; log ε = 4·1 (in *cyclo*hexane)] is very close to that of dihydroagnosteryl acetate ($\lambda_{max.}$ = 243 mμ.; log ε = 4·2) as also is the specific rotation.

Furthermore although the m. p. (149—151°) is low compared with that of pure dihydroagnosteryl acetate (m. p. 167·5°), brief treatment with selenium dioxide in glacial acetic acid gave pure dihydroagnosteryl acetate, m. p. 167—168°, $[\alpha]_D^{18}$ +87·0°, a direct comparison between the two confirming their identity.

The compound also gave an intense yellow colour with tetranitromethane, whereas the β-isomer, like that described by Ruzicka *et al.* (*loc. cit.*), gives no colour with this reagent.

When dihydroagnosteryl acetate was oxidized with chromic acid under the conditions described by Marker for dihydrolanosteryl acetate, it was found that very rapid oxidation took place and the sole product isolated was diketodihydrolanosteryl acetate. This simple oxidation probably accounts for the variation in yields of crude dihydroagnosteryl acetate obtained in the oxidation of dihydrolanosteryl acetate, since in the time interval between the completion of the reaction and the dilution of the reaction mixture with water rapid oxidation of the dihydroagnosteryl acetate could take place to give diketodihydrolanosteryl acetate.

The identity of the more soluble compound, obtained from the mother liquors of the oxidation of dihydrolanosteryl acetate (apparently identical with Marker's β-ketodihydrolanosteryl acetate), with the ketodihydrolanosteryl acetate prepared by Ruzicka's (*loc. cit.*) method was indicated by analytical data, mixed melting-point determination, and by a comparison of physical constants.

	M. p.	$[\alpha]_D^{18}$.	$\lambda_{max.}$	log ε.
Ketodihydrolanosteryl acetate	151·5—152·5°	+21·3°	255 mμ.	4·08 (in alcohol)
Chromic acid oxidation product (β-isomer)	151—152°	+22·9°	257 mμ.	4·1 (in alcohol)

This ketodihydrolanosteryl acetate when treated with selenium dioxide in glacial acetic acid under conditions analogous to those used for the conversion of dihydrolanosteryl acetate into dihydroagnosteryl acetate gave a product, m. p. 195—196°, $[\alpha]_D^{18}$ +67·7°, provisionally designated as a ketodidehydro-acetate. The ketodidehydro-acetate gave a yellow colour with tetranitromethane and from the analytical figures it would appear probable that two more ethylenic linkages have been introduced into the molecule with the formation of a trienone.

Muhr (Thesis, Zurich, 1945) has described a compound, m. p. 194·5—195·5°, $[\alpha]_D^{18}$ +65·4° (ultra-violet absorption spectrum: $\lambda_{max.}$ = 260 and 330—335 mμ.; log ε = 3·91), which was isolated from the mother liquors remaining after the removal of dihydroagnosteryl acetate obtained by the oxidation of dihydrolanosteryl acetate with selenium dioxide. The analytical data recorded for this compound agreed closely with those found for our ketodidehydro-acetate. Surprisingly enough Muhr's compound was formulated as an unsaturated diketo-alcohol ($C_{30}H_{44}O_3$ or $C_{30}H_{46}O_3$). It was tentatively suggested that in the course of chromatographic purification upon alumina deacetylation had occurred, although all attempts to reacetylate the compound failed.

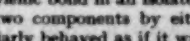
Our experiments have shown that it is possible to convert dihydroagnosteryl acetate into ketodihydrolanosteryl acetate, by perbenzoic acid, and that selenium dioxide oxidizes this further to the ketodidehydro-acetate. The formation of the compound obtained by Muhr can receive a simple explanation by regarding it as the ketodidehydro-acetate, $C_{32}H_{48}O_3$, formed by simultaneous dehydrogenation and introduction of an oxygen atom by the selenium dioxide.

The ultra-violet absorption spectrum of the ketodehydro-acetate is also compatible with the formulation as a trienone, but insufficient spectral data are available for a direct comparison with similar derivatives of known structure in the sterol and triterpene series. It is true that dienones in general have their principal maxima at a lower wave-length, but calculations from the data given by Fieser (" Natural Products related to Phenanthrene " 3rd Edn., 1949, p. 192) show that a dienone having both conjugated double bonds between substituted carbon atoms would possess a similar absorption maximum.

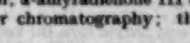
The presence of two maxima in the spectrum of an αβ-unsaturated ketone has previously

been reported by Ewen, Gillam, and Spring (*J.*, 1944, 29), α-amyradienone III having maxima at 260 and 292 mμ. These authors suggested that a possible explanation was the formation of mixed crystals of the dienone containing the new double bond with an isomer having the newly introduced ethylenic bond in an isolated position. However, α-amyradienone III could not be resolved into two components by either crystallization or chromatography; the lanosterol derivative similarly behaved as if it was homogeneous.

It seems certain, however, that the original conjugated system in ketodihydrolanosteryl acetate has been extended by the introduction of at least one double bond. One can also infer that the carbon atoms αβ to the original unsaturated centres in ketodihydrolanosteryl acetate must carry at least one hydrogen atom each to allow for the formation of the ketodehydro-



(I.)



(II.)

acetate. Ketodihydrolanosteryl acetate would, therefore, contain the system (I) which could then react to form the ketodehydro-acetate containing the system (II).

Experimental.

[M. p.s are uncorrected. All rotations were determined in chloroform solution. The solvent is specified where the ultra-violet spectrum was not determined in alcohol, the values are then corrected to this solvent by applying the necessary correction as described by Fieser (*loc. cit.*) for αβ-unsaturated ketones.]

Oxidation of Dihydroagnosteryl Acetate.—A solution of dihydroagnosteryl acetate (7 g.) in ice-cold chloroform (30 ml.) was treated at 0° with a chloroform solution of perbenzoic acid (equivalent to 0·4 g. of active oxygen). After 40 hours the excess of oxidizing agent was destroyed by the addition of a solution of potassium iodide, the mixture was acidified, and the iodine was removed by shaking with 0·1*N*-thiosulphate solution. The chloroform layer was washed twice with 2*N*-sodium hydroxide solution and then with water, the solution was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residual oil was dissolved in methanol (50 ml.) and the solution heated under reflux for ten minutes; on cooling, a white powder (4·5 g.), m. p. 145—148°, separated and was filtered off. This, after two further crystallizations from chloroform–methanol, had m. p. 151—152°, $[\alpha]_D^{18}$ +26·0° (*c*, 0·151). Recrystallization led to a gradual rise in the melting point, and a solution of the solid (3 g.) in light petroleum (b. p. 60—80°; 300 ml.) was therefore chromatographed on a column of alumina (150 g.) (Peter Spence, grade H, 100—200 mesh). Elution of the column gave the following fractions:

Fraction.	Eluate.	Product.
(*a*)	200 ml. of light petroleum (b. p. 60—80°) + 50 ml. of benzene	0·2 g. of solid.
(*b*)	200 ml. of light petroleum (b. p. 60—80°) + 50 ml. of benzene	0·1 g. ,,
(*c*)	100 ml. of light petroleum (b. p. 60—80°) + 100 ml. of benzene	0·5 g. ,,
(*d*)	100 ml. of light petroleum (b. p. 60—80°) + 100 ml. of benzene	2·0 g. ,,
(*e*)	200 ml. of benzene	trace of oil.

Fractions (a) *and* (b). These were bulked and on recrystallization from ethyl acetate–methanol gave white needles (0·25 g.), m. p. 184° (Found: C, 79·0; H, 10·8. Calc. for $C_{32}H_{54}O_3$: C, 79·3; H, 10·8%). Ultra-violet spectrum: no absorption above $E_{1cm}^{1\%}$ = 30 in *cyclo*hexane.

Fractions (c) *and* (d). Recrystallization from chloroform–methanol gave long, white needles (2·0 g.), m. p. 151—152°, $[\alpha]_D^{18}$ +24·0° (*c*, 0·0495) (Found: C, 79·3; H, 10·9. Calc. for $C_{32}H_{54}O_3$: C, 79·3; H, 10·8%). Ultra-violet spectrum: $\lambda_{max.}$ = 245 mμ.; log ε = 4·1, in *cyclo*hexane; corresponding to $\lambda_{max.}$ = 256 mμ. in alcohol.

A mixture of this compound with authentic ketodihydrolanosteryl acetate prepared according to Ruzicka *et al.* (*loc. cit.*) had m. p. 151—152°.

Hydrolysis. Saponification of the acetate with 5% alcoholic potash for two hours gave the alcohol ketodihydrolanosterol, m. p. 136°, $[\alpha]_D^{18}$ +28·5° (*c*, 0·0666). Reacetylation gave the acetate, m. p. 151—152°, which gave no depression in m. p. with the original acetate.

Isolation of the Product from the Mother Liquors by Methanol Treatment.—Evaporation of the methanol gave a glassy resin; this was dissolved in glacial acetic acid (50 ml.) and treated at the boiling point with six drops of concentrated sulphuric acid. The mixture was heated for a further 15 minutes on the water-bath and then poured into ice-water. The separated solids (1·5 g.) were filtered off, dried, and recrystallized from ethyl acetate–methanol, and had m. p. 184°. Three further crystallizations from aqueous methanol gave colourless needles, m. p. 205°, $[\alpha]_D^{18}$ +96·3° (*c*, 0·0160) (Found: C, 76·6; H, 10·7. $C_{32}H_{52}O_4$ requires C, 76·8; H, 10·4%). Ultra-violet spectrum: no high intensity absorption in *cyclo*hexane, weak absorption at 267 mμ. due probably to traces of impurity. This *compound* is extremely soluble in methanol, chloroform and ethyl acetate.

Chromic acid Oxidation of Dihydrolanosteryl Acetate according to Marker et al.—To a solution of dihydrolanosteryl acetate (15 g.) in glacial acetic acid (450 ml.) at 80° was added a solution of chromic acid (4·5 g.) in 90% acetic acid (50 ml.). The mixture was heated at 80° for a further 10 minutes and then poured into water (150 ml.); this was extracted with ether, and the ethereal extract was washed twice with 10% sodium carbonate solution and twice with water, and dried (Na_2SO_4). The residue, after removal of the ether, was dissolved in glacial acetic acid (200 ml.); on cooling to room temperature a small amount of gelatinous material separated and was filtered off; overnight the filtrate deposited a

crystalline solid (2 g.), m. p. 130° (Marker *et al.* reported that 4 g. separated from 250 ml. of acetic acid). Repeated crystallization from ethyl acetate, methanol, acetone, and ethyl alcohol caused a gradual rise in m. p. to the value 149—150° recorded by Marker *et al.* Purification by this process is very wasteful and chromatography gave no better results, the overall yield being 0·4—0·5 g. (Found: C, 82·15; H, 11·5. Calc. for $C_{32}H_{52}O_4$: C, 82·0; H, 11·2%). The material had $[\alpha]_D^{18}$ +80·0° (*c*, 0·0472). Ultra-violet spectrum: $\lambda_{max.}$ = 242 mμ., log ε = 4·1 (in *cyclo*hexane).

The acetic acid filtrate from the first crystallization was evaporated to dryness in a vacuum and the residue recrystallized from ethyl acetate to give a product (2 g.), m. p. 148°. This was recrystallized from acetone until the m. p. had risen, after four further crystallizations, to 151—152°, giving 1·5 g. of product, $[\alpha]_D^{18}$ +22·9° (*c*, 0·0532) (Found: C, 78·9; H, 10·8. Calc. for $C_{32}H_{54}O_3$: C, 79·3; H, 10·8%). Ultra-violet spectrum: $\lambda_{max.}$ = 246 mμ.; log ε = 4·1 (inflexion at 252 mμ.) in *cyclo*hexane; corresponding to $\lambda_{max.}$ = 257 mμ. in alcohol.

From the mother liquors pure diketodihydrolanosteryl acetate (1 g.), m. p. 157·5°, $[\alpha]_D^{18}$ +90·0° (*c*, 0·0491), was obtained together with some unchanged dihydrolanosteryl acetate.

Dehydrogenation of Ketodihydrolanosteryl Acetate.—Selenium dioxide (0·5 g.) was added to a solution of ketodihydrolanosteryl acetate (1 g.) in glacial acetic acid (100 ml.). The solution was refluxed for 2½ hours and then filtered from the black selenium which had separated, and the filtrate poured into water. The precipitated solids were extracted with ether (2 × 200 ml.), and the ether extract was washed successively with 2*N*-sodium hydroxide solution and water. The ether extract, after being dried (Na_2SO_4), was evaporated, and the residual solid in light petroleum (b. p. 60—80°; 200 ml.) was percolated through a column of alumina (40 g.). Evaporation of the filtrate gave no solid residue.

The column was eluted:

(*a*) 200 ml. of light petroleum (b. p. 60—80°) gave a trace of yellow oil insoluble in methanol; (*b*) 500 ml. benzene gave 0·75 g. of solid; (*c*) 200 ml. chloroform gave 0·1 g. of oil.

Fraction (*b*) was crystallized from acetone (20 ml.)–methanol (50 ml.) and gave glistening needles (0·65 g.), m. p. 195°. Further crystallization gave a pure *product* (0·5 g.), m. p. 195—196°, $[\alpha]_D^{18}$ +67·7° (*c*, 0·0293) (Found: C, 80·0; H, 10·0. $C_{32}H_{48}O_3$ requires C, 79·9; H, 10·1. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·45%). Ultra-violet spectrum: $\lambda_{max.}$ = 256 and 327 mμ.; log ε = 3·9, in alcohol. The compound is readily soluble in chloroform and acetone, but sparingly soluble in methanol. It gives an intense yellow colour with tetranitromethane.

The authors are indebted to Dr. E. A. Braude for the ultra-violet absorption spectra, and to Mr. P. Barker for the specific rotations. They gratefully acknowledge the advice and criticism of Professor H. Burton.

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255. *Thermal Cyclization of o-Aroyloxyacetoarones. A New Synthesis of Flavones.*

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o-Aroyloxyacetoarones (II) yield flavones (VII) when heated in glycerol. The method is applicable to the synthesis of flavonols. If glycerol is replaced by benzoic anhydride, 3-benzoylflavones (IX) are obtained. It is believed that a thermally produced Baker–Venkataraman transformation is involved in the cyclization.

The fusion of *o*-hydroxyacetophenones (I) or of *o*-aroyloxyacetophenones (II) with an aromatic acid anhydride and the sodium salt of the corresponding acid (Allan–Robinson reaction) has been extensively used in the synthesis of flavones (VII). The method suffers from the disadvantage that a 3-aroylflavone (IX) is often formed, and that loss occurs in subsequent hydrolysis to the flavone (see Baker and Butt, *J.*, 1949, 2142). It has now been found [see also Bernfeld and Wheeler, *J.*, 1949, pp. 1916 (footnote) and 1917] that thermal cyclization of *o*-aroyloxyacetophenones to flavones can be effected by heating them in anhydrous glycerol (10—20 parts) at about 250° for at least 30 minutes. The product is recovered by dilution with water. The optimum conditions for each ester require to be determined, but it is important that the glycerol employed should be rendered anhydrous by prior distillation under reduced pressure. Addition of a variety of acid and basic catalysts, *e.g.*, boric acid (cf. Duff, *J.*, 1941, 547), phenol, anhydrous sodium carbonate, or potassium cyanide, did not improve the yield, nor was any successful result obtained by replacement of glycerol by liquid paraffin or diphenyl ether.

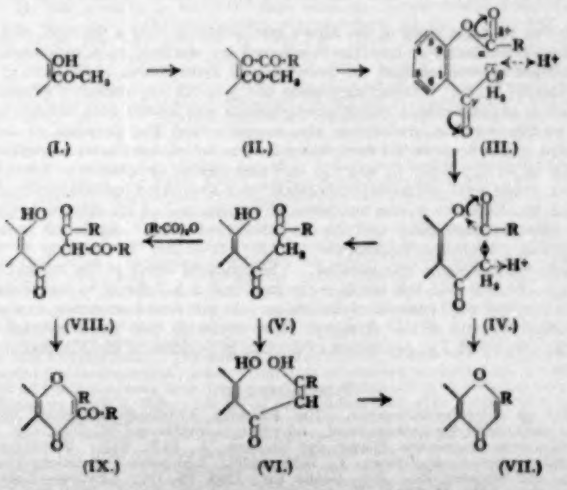
Flavones produced by Thermal Cyclization.—The flavones which have been prepared by this new method are listed in Tables IV and V. Yields obtained by the Baker–Venkataraman process, which is of recognized value in the synthesis of flavones, are given for comparison,

but it should be noted that the yields given for either method are not necessarily the best obtainable. Additional ester groups present in the acetoarone nucleus may be hydrolysed in the cyclization; for example, resacetophenone dibenzoate (No. 7, Table V) gave 7-hydroxyflavone. Work in progress indicates that diflavones can be prepared by thermal cyclization, in glycerol, of diacetylresorcinol esters. The method may also be of use in the synthesis of flavonols; ω-methoxyresacetophenone dibenzoate (No. 11, Table V) gave 7-hydroxy-3-methoxyflavone (39% yield). This flavonol ether was also obtained (32% yield) by the action of a base (potassium carbonate in pyridine) on the ester, the diketone formed cyclizing at once. This seems to be the first direct application of the Baker–Venkataraman method to the synthesis of a flavonol derivative, though Chavan and Robinson's conversion (*J.*, 1933, 368) of ω : 2 : 4 : 6-tetrabenzoyloxyacetophenone into 3 : 5 : 7-tribenzoyloxyflavone by the action of potassium acetate in boiling alcohol probably involves this transformation.

Mechanism of Cyclization.—The yields obtained by the new method vary greatly with the ester taken (see Tables IV and V). A comparison of these yields (Table I), however, indicates that they tend to increase with the acid strength of R·CO_2H (see II), the acetoarone nucleus remaining unchanged. This trend in the yields suggests that the mechanism of reaction involves the positive polarization of $C_{(\omega)}$ of (III).

The results of experiments in which glycerol was replaced by benzoic anhydride are also important in relation to the course of the cyclization. Unexpectedly, it was found that at the boiling point (>300°) of the anhydride, cyclization was accompanied by 3-aroylation. Thus o-benzoyloxyacetophenone when heated under reflux with benzoic anhydride gave 3-benzoylflavone, and resacetophenone dibenzoate and phloroacetophenone tribenzoate yielded, respectively, 7-benzoyloxy- and 5 : 7-dibenzoyloxy-3-benzoylflavone. Hitherto a basic catalyst, *e.g.*, the sodium salt related to the acid anhydride, or triethylamine (Kuhn and Löw, *Ber.*, 1944, **77**, *B*, 202), has been regarded as essential for Allan–Robinson aroylation of o-hydroxy- or o-aroyloxy-acetoarones to 3-aroylflavones, but these new results indicate that if the temperature is sufficiently high a catalyst is not required. In this connexion a new method for the removal of benzoic anhydride is described in the experimental section (*E*).

Baker (*J.*, 1933, 1381) showed that the aroylation in question involves the transformation which bears his name. The proposed thermal-cyclization mechanism set out in (III) ⟶ (IX) is similar to that proved by Baker for Allan–Robinson aroylation, but includes the interpretation of his transformation suggested by Doyle *et al.* (*Proc. Roy. Dublin Soc.*, 1948, **24**, 291). At the



high temperatures employed, a proton on $C_{(\beta)}$ of (III) activated by the keto-group ($C_{(\gamma)}$) may through thermal vibration ionize sufficiently to enable an incipient $C_{(\beta)}$–$C_{(\omega)}$ bond to be formed.

The tendency to bond formation will increase with the positive polarization of $C_{(\alpha)}$, that is, with the strength of R·CO_2H.

TABLE I.

Yields of flavones obtained by thermal cyclization of esters from acids and phenols.

		Phenolic component and corresponding yields (%).[1]			
Acid.	$A \times 10^5$.	*o*-Hydroxyacetophenone.	2-Hydroxy-5-methoxyacetophenone.	1-Hydroxy-2-acetonaphthone.	5-Hydroxy-6-acetylindane.
Acetic	1·8	No cyclization	—	—	—
p-Anisic	3·2	—	7 [2,3]	10	—
Cinnamic	3·5	—	5	Trace; 1 hr.; 230°	—
Benzoic	6·5	49; 54 (c); 120 mins.; 200°	5 [3]	56	50 (c)
p-Chlorobenzoic	9·3	—	21	70	—
m-Nitrobenzoic	35	43 (c); 120 mins.	—	—	—
p-Nitrobenzoic	42	70 (c); 120 mins.	23	*ca.* 80	66 (c)
3 : 5-Dinitrobenzoic	157	67 (c)	29	—	—
o-Nitrobenzoic	656	70 (c); 120 mins.; 200°	—	—	—

[1] (c) indicates yield of crude product before crystallization; otherwise the yield of crystallized product is given. [2] The glycerol used in this cyclization was of greater than 98% purity but not specially dehydrated; this may have reduced the yield. [3] If not stated, heating was for 30 minutes at 250°.

As the $C_{(\beta)}$–$C_{(\alpha)}$ bond forms, the $C_{(\alpha)}$–O single bond lengthens as in a normal Claisen condensation between an ester and a methyl ketone, with formation of the Baker–Venkataraman transition compound (IV). This may cyclize at once to (VII)—the literature contains numerous instances of the direct formation of flavones in the Baker–Venkataraman rearrangement. It will be seen that an internal aldol type of condensation is involved. Alternatively, (IV) may, as in the normal base-catalyzed transformation, pass into the diketone (V and VI) which in the absence of benzoic anhydride cyclizes at the high temperatures employed to (VII). Doyle *et al.* (*loc. cit.*) give examples of *o*-hydroxy-diketones which cyclize to flavones on being heated above the melting point and the mechanism of cyclization has been discussed by Nowlan *et al.* (*J.*, 1950, 340). In presence of benzoic anhydride, however, aroylation of (V) occurs as postulated by Baker (*loc. cit.*) to form the triketone (VIII) which cyclizes to the 3-aroylflavone (IX).

It will be noted that the basis of the above mechanism is that a thermal, and not a base-catalyzed, Baker–Venkataraman reaction is effected by working at a sufficiently high temperature. It should be recalled that the possibility of 3-aroylation of (VII) to give (IX) was eliminated by Baker (*loc. cit.*). Direct aroylation of $C_{(\beta)}$ in (III) is unlikely; dibenzoylmethane was not isolated in experiments in which acetophenone was heated with benzoic anhydride.

This view of the reaction mechanism also suggests that the presence of anionoid (*e.g.*, methoxyl) groups in positions in the acetoarone nucleus which facilitates neutralization of $C_{(\alpha)}$ (III; C_3 and C_5) or of $C_{(\gamma)}$ (III; C_4 and C_6) will also hinder cyclization. Actually as shown in Table I, poor yields were obtained with esters of 2-hydroxy-5-methoxyacetophenone, and (see nos. 19 and 20, Table V) in the synthesis of chrysin and of its dimethyl ether from the benzoates of phloroacetophenone and its 4 : 6-dimethyl ether. Again, it was not found possible to cyclize *o*-acetoxyacetophenone (cf. II; R = Me) by heating it in glycerol; neither chromone nor coumarin was isolated. The anionoid effect of the methyl group tends to neutralize $C_{(\alpha)}$. In line with this result is the fact that it is difficult to transform *o*-acetoxyacetophenone into *o*-hydroxybenzoylacetylmethane. It was found necessary to use as catalyst triphenylmethylsodium, one of the strongest bases available (see Experimental, section *C*). The bases usually employed, *e.g.*, potassium hydroxide in pyridine or metallic sodium in toluene, were ineffective.

EXPERIMENTAL.

A. *Preparation of o-Hydroxyacetoarones.*—The following *o*-hydroxyacetoarones were prepared according to the methods of the authors cited: *o*-hydroxyacetophenone (Mozingo, *Org. Synth.*, 1941, **21**, 43); 6-methoxyresacetophenone (Slater and Stephen, *J.*, 1920, 312); 2-hydroxy-5-methoxyacetophenone (Baker, Brown, and Scott, *J.*, 1939, 1926); 2-hydroxy-4 : 6-dimethoxyacetophenone (Belton, Nowlan, and Wheeler, *Proc. Roy. Dublin Soc.*, 1949, **25**, 19); 1-hydroxy-2-acetonaphthone (Witt and Braun, *Ber.*, 1914, **47**, 3216; Nowlan, Slavin, and Wheeler, *J.*, 1950, 340); 5-hydroxy-6-acetylindane (Baker, *J.*, 1937, 478). Phloroacetophenone was synthesised by the action of acetic anhydride and sulphuric acid on phloroglucinol (Israelstam and Stephen, *J. S. African Chem. Inst.*,

1943, **26**, 41), but the method in our hands was unreliable. The Hoesch synthesis (Gulati, Seth, and Venkataraman, *Org. Synth.*, 1943, Col. Vol. II, p. 522) was found preferable.

B. *Preparation of Esters of o-Hydroxy-ketones.*—The esters, *o*-acetoxyacetophenone excepted (see below), were prepared by the pyridine–acid chloride method (Doyle *et al.*, *Proc. Roy. Dublin Soc.*, 1948, **24**, 299; Nowlan *et al.*, *loc. cit.*), the yields being usually over 90%. Reference numbers (in parentheses in the text) have been inserted to facilitate cross-reference. *Esters* prepared for the first time are listed in Table II.

TABLE II.

New esters of o-hydroxy-ketones.

Ester no.	Ester.	M. p.	Formula.	Found, %. C.	H.	Cl or S.	Required, %. C.	H.	Cl or S.
8	Resacetophenone di-(*p*-chlorobenzoate)	116—118°	$C_{22}H_{14}O_4Cl_2$	61·8	3·3	Cl, 16·4	61·5	3·3	Cl, 16·6
10	Resacetophenone dicinnamate	114—116	$C_{26}H_{20}O_4$	75·9	4·9	—	75·7	4·9	—
13	2-(*p*-Chlorobenzoyloxy)-5-methoxyacetophenone	116—117	$C_{16}H_{13}O_4Cl$	62·7	4·1	Cl, 11·7	63·1	4·3	Cl, 11·7
16	2-(*p*-Anisoyloxy)-5-methoxyacetophenone	94—95	$C_{17}H_{16}O_5$	68·0	5·2	—	68·0	5·3	—
18	2-(Toluene-*o*-sulphonyloxy)-5-methoxyacetophenone	82—83	$C_{16}H_{16}O_5S$	60·1	4·8	S, 9·9	60·0	5·0	S, 10·0
21	2-Cinnamoyloxy-4 : 6-dimethoxyacetophenone	99	$C_{19}H_{18}O_5$	69·8	5·6	—	69·9	5·5	—
22	*o*-Benzoyloxypropiophenone	58—61 (Methyl alcohol)	$C_{16}H_{14}O_3$	75·4	5·4	—	75·6	5·5	—
24	1-(*p*-Chlorobenzoyloxy)-2-acetonaphthone	129—130	$C_{19}H_{13}O_3Cl$	69·8	4·0	Cl, 11·2	70·3	4·0	Cl, 10·9
26	1-(*p*-Anisoyloxy)-2-acetonaphthone	125—130 (Acetic acid)	$C_{20}H_{16}O_4$	75·2	5·1	—	75·0	5·0	—

These compounds except as otherwise indicated in the m. p. column were crystallized from alcohol All formed colourless to pale yellow crystals.

Esters which have previously been prepared. *o*-Acetoxyacetophenone (1)(Friedlaender and Neudörfer, *Ber.*, 1897, **30**, 1080) was obtained by use of pyridine and acetic anhydride. The yield (70% calc. on *o*-hydroxyacetophenone) of *o*-benzoyloxyacetophenone (2) obtained by Doyle *et al.* (*loc. cit.* p. 304; cf. Baker, *J.*, 1933, 1386) was increased to 83% by using 1·5 mols. of benzoyl chloride in place of 1 mol. The following were also prepared: *o*-(2-nitrobenzoyloxy)acetophenone (3) (Doyle *et al.*, *loc. cit.*); *o*-(3-nitrobenzoyloxy)acetophenone (4), m. p. 91—93° (from alcohol or ligroin) [Virkar (*J. Univ. Bombay*, 1942, **11**, 136) gives m. p. 99—100° (from alcohol)]; *o*-(4-nitrobenzoyloxy)acetophenone (5) (Doyle *et al.*, *loc. cit.*); *o*-(3 : 5-dinitrobenzoyloxy)acetophenone (6), m. p. 138—140° (from aqueous alcohol) [Doyle *et al.* (*loc. cit.*) give m. p. 131—133° (from alcohol–acetone)]; resacetophenone dibenzoate (7) and resacetophenone di-(*p*-anisoate) (9) (Baker, *loc. cit.*); ω-methoxyresacetophenone dibenzoate (11) (Fonseka, *J.*, 1947, 1683) (Found: C, 70·8; H, 4·7. Calc. for $C_{23}H_{18}O_6$: C, 70·8; H, 4·6%); 2-benzoyloxy-5-methoxyacetophenone (12), 2-(*p*-nitrobenzoyloxy)-5-methoxyacetophenone (14), 2-(3 : 5-dinitrobenzoyloxy)-5-methoxyacetophenone (15) and 2-cinnamoyloxy-5-methoxyacetophenone (17) (Doyle *et al.*, *loc. cit.*); phloroacetophenone tribenzoate (19) (Canter, Curd, and Robertson, *J.*, 1931, 1248); 2-benzoyloxy-4 : 6-dimethoxyacetophenone (20) (Gulati and Venkataraman, *J.*, 1936, 268); 1-benzoyloxy-2-acetonaphthone (23) (Bhullar and Venkataraman, *J.*, 1931, 1168); 1-(*p*-nitrobenzoyloxy)-2-acetonaphthone (25) (Virkar, *loc. cit.*); 1-cinnamoyloxy-2-acetonaphthone (27) (Bhalla, Mahal, and Venkataraman, *J.*, 1935, 870); 2-benzoyloxy-3-acetonaphthone (28); 5-benzoyloxy-6-acetylindane (29) and 5-(*p*-nitrobenzoyloxy)-6-acetylindane (30) (Nowlan *et al.*, *loc. cit.*).

C. *Preparation of o-Hydroxydiaroylmethanes (Table III).*—The Baker–Venkataraman transformation was carried out as follows (see Doyle *et al.*, *loc. cit.*): A solution of the ester in pyridine (10—20 parts) was heated under reflux (for 15 minutes unless otherwise stated in Table III) with the transforming agent shown in that Table. The resulting mixture was cooled, diluted with water, and acidified with 10% hydrochloric or acetic acid to precipitate the yellow diketone which, if solid, was recovered by filtration. Otherwise the product was extracted with ether and the extract was washed with aqueous sodium hydrogen carbonate and with 2% aqueous sodium hydroxide. The diketone was precipitated from the alkali hydroxide solution by saturation with carbon dioxide and was re-dissolved in ether. The ethereal solution was washed with water and dried (Na_2SO_4). The residue from the evaporation of the solvent was recrystallized. The new *diketones* obtained in this way are set out in Table III.

Transformation of o-acetoxyacetophenone. A solution of triphenylmethylsodium in absolute peroxide-free ether (200 ml.) was prepared from triphenylchloromethane (16 g.) by Hauser and Hudson's procedure (*Org. Reactions*, 1942, **1**, 286). 150 Ml. of this solution were added in an atmosphere of nitrogen to an anhydrous ethereal solution of *o*-acetoxyacetophenone (ester No. 1) (5 g. in 100 ml.). The yellow precipitate formed was collected after 1 hour and extracted with boiling water (300 ml.) in small successive quantities. The total aqueous extract was acidified with 10% acetic acid and the precipitate formed was dissolved in ether. The ethereal solution was dried (Na_2SO_4) and the solvent evaporated off. The residue (0·3 g.) when twice crystallized from benzene–ligroin formed white needles, m. p. 91—92°, not depressed by admixture with an authentic specimen of *o*-hydroxybenzoylacetylmethane prepared by a Claisen condensation of *o*-hydroxyacetophenone and ethyl acetate as described by Wittig (*Annalen*, 1926, **446**, 169).

TABLE III.

New o-Hydroxydiaroylmethanes.

Corresponding ester no.	Diketone.	M. p.	Formula.	Elements.	Found, %.	Required, %.	Yield of crystallised diketone.
8	4-Chloro-2′-hydroxy-4′-(*p*-chlorobenzoyloxy)dibenzoylmethane	205—207°	$C_{28}H_{14}O_5Cl_2$	C	60·9	61·5	14 [a]
				H	3·4	3·3	
				Cl	16·7	16·6	
13	4-Chloro-2′-hydroxy-5′-methoxydibenzoylmethane	100—101	$C_{16}H_{13}O_4Cl$	C	62·9	63·1	90 [b]
				H	4·5	4·3	
				Cl	11·7	11·7	
16	2-Hydroxy-5 : 4′-dimethoxydibenzoylmethane	123—125	$C_{17}H_{16}O_4$	C	67·7	68·0	80 [b]
				H	5·2	5·2	
21	2-Hydroxy-4 : 6-dimethoxybenzocylcinnamoylmethane	126	$C_{19}H_{18}O_5$	C	69·8	69·9	14 [b]
				H	5·6	5·5	
24	4-Chlorobenzoyl-1′-hydroxy-2′-naphthoylmethane	178—180	$C_{18}H_{11}O_3Cl$	C	70·3	70·3	60 [b]
				H	4·1	4·0	
				Cl	11·0	10·9	
26	*p*-Anisoyl-1-hydroxy-2-naphthoylmethane	135—137	$C_{19}H_{14}O_4$	C	74·5	75·0	60 [b]
				H	5·2	5·0	

These compounds, No. 8 excepted, were recrystallised from alcohol. No. 8 was recrystallised from acetone.

[a] Transforming agent, anhydrous potassium carbonate (2·2 mols.); time of heating 2 hours. [b] Transforming agent, ethyl sodioacetoacetate (excess). [c] Transforming agent, powdered potassium hydroxide (1—2 mols.).

TABLE IV.

New flavones obtained from the corresponding esters (Table II) by cyclization in glycerol (method 1) or through the corresponding diketones (Table III) (method 2).

Corresponding ester no.	Pyrone formed. [a]	M. p.	Formula.	Elements.	Found, %.	Required, %.	Yield (%) of pyrone from ester, method 1.	Yield (%) of pyrone from ester, method 2.
8	4′-Chloro-7-hydroxyflavone	277—278°	$C_{15}H_9O_3Cl$	C	65·6	66·1	23	11 [b]
				H	3·6	3·3		
				Cl	13·1	13·0		
13	4′-Chloro-6-methoxyflavone	175—177	$C_{16}H_{11}O_3Cl,H_2O$ [c]	C	63·4	63·1	21	60
				H	4·3	4·3		
				Cl	11·7	11·7		
16	6 : 4′-Dimethoxyflavone	194—195	$C_{17}H_{14}O_4$	C	72·5	72·3	7 [d]	40
				H	5·1	5·0		
22	3-Methylflavone	66—67 [e]	$C_{16}H_{12}O_2$	C	80·7	81·4	21	Ester did not transform.
				H	5·2	5·1		
24	4′-Chloro-α-naphthaflavone	236—238	$C_{19}H_{11}O_3Cl$	C	74·3	74·4	70	50
				H	3·6	3·6		
				Cl	11·5	11·6		

[a] These compounds were colourless to pale yellow. 3-Methylflavone was recrystallized from light petroleum (b. p. 40—60°), and the other flavones from alcohol. The time and temperature of heating in glycerol for 3-methylflavone were 2 hours and 260°. The conditions for the other flavones were 30 minutes and 250°. The proportion of ester to glycerol was 1 : 20, except with nos. 8 and 22 when it was 1 : 10. [b] The yield in the transformation of this ester was low (see No. 8, Table III). Cyclization was effected in this instance by dissolving the diketone in three parts of concentrated sulphuric acid and diluting the mixture with water after 30 minutes. Hydrolysis of the 4′-(*p*-chlorobenzoyloxy)-group in the diketone [4-chloro-2′-hydroxy-4′-(*p*-chlorobenzoyloxy)dibenzoylmethane] occurred during the cyclization (see Baker, *J.*, 1933, 1382, and footnote 6, Table V). [c] This flavone contained one mol. of water of crystallization (cf. Bernfeld and Wheeler, *J.*, 1949, 1918). [d] The glycerol used with this ester was not specially dehydrated; it contained over 98% of glycerol. [e] The mixture obtained by pouring the glycerol solution into water was kept at 0° for 48 hours and extracted with ether. The ethereal solution was washed with 2% aqueous potassium hydroxide, and with water, and was dried (Na_2SO_4). The solvent was evaporated off and the residue was recrystallized from light petroleum (b. p. 40—60°) to yield colourless crystals, m. p. 66—67°, which did not depress the m. p. (72—74°) of an authentic specimen of 3-methylflavone prepared by the Allan–Robinson aroylation method (see below).

It was not found possible to transform 2-(toluene-*o*-sulphonyloxy)-5-methoxyacetophenone (ester No. 18) or *o*-benzoyloxypropiophenone (ester No. 22).

D. *Preparation of 4-Pyrones* (Tables IV and V).—These compounds were obtained from the esters of the *o*-hydroxy-ketones by the following methods:

Method 1. *Direct cyclization of o-aroyloxyacetoarones.* The ester was heated in glycerol (10—20 parts; previously distilled at 1 mm.) for the time and at the temperature shown in Tables IV and V,

TABLE V.

Known pyrones obtained from the corresponding esters (*o*-acyloxyacetoarones) by cyclization in glycerol (method 1). Yields obtained by application of the Baker–Venkataraman transformation and cyclization of the resulting diketones (method 2) are given for comparison

Corresponding ester no. and experimental details, if not 30 minutes, 250°, and 10 parts of glycerol.	Pyrone formed.	Confirmation of identity of product obtained by method 1.[1]	Yield (%) [2] of pyrone from ester. See section D above: method 1.	method 2.
No. 2; 120 mins.; 260°	Flavone [3]	A.S. (method 2)	49 [4] 54 [5]	80 [6] —
No. 3; 120 mins.; 200°	2′-Nitroflavone [3]	M. p. (*a*)	70 [5]	40 [5] (*a*)
No. 4; 120 mins.	3′-Nitroflavone [3]	M. p. (*a*)	43 [5]	45 [5] (*b*)
No. 5; 120 mins.	4′-Nitroflavone [3]	M. p. (*a*)	70 [5]	38 [5] (*a*)
No. 6	3′ : 5′-Dinitroflavone	M. p. (*a*)	67 [5]	—
No. 7	7-Hydroxyflavone	A.S. (*c*)	53	48 [6]
No. 9	7-Hydroxy-4′-methoxyflavone (pratol)	M. p. and m. p. of acetyl derivative in agreement with (*c*)	16 [5]	22 (*c*)
No. 11	7-Hydroxy-3-methoxyflavone	A.S. (*d*)	30	32 (method 3); see below
No. 12; glycerol (20 parts)	6-Methoxyflavone	A.S. (*a*)	5 [7]	53 (*a*)
No. 14; glycerol (20 parts)	4′-Nitro-6-methoxyflavone	A.S. (*a*)	23	18 (*a*)
No. 15; glycerol (20 parts)	3′ : 5′-Dinitro-6-methoxyflavone	A.S. (*a*)	20	53 (*a*)
No. 17; glycerol (20 parts)	6-Methoxy-2-styrylchromone	A.S. (*a*)	5	48 (*a*)
No. 19	5 : 7-Dihydroxyflavone (chrysin)	M. p. (*e*) [8]	7	—
No. 20; 60 mins.; 220°; glycerol (5 parts)	5 : 7-Dimethoxyflavone	A.S. (*f*) [8]	Trace	43 (*f*)
No. 23; glycerol (20 parts)	α-Naphthaflavone [9]	A.S. (*g*)	56	26 (*h*)
No. 25; glycerol (20 parts)	4′-Nitro-α-naphthaflavone	M. p. (*b*)	*ca.* 80	80 (*b*); cf. (*i*)
No. 26; glycerol (20 parts)	4′-Methoxy-α-naphthaflavone	A.S. (method 2); m. p. (*g*)	10	50 (see Table III)
No. 27; 60 mins.; 230°; glycerol (20 parts)	2-Styryl-7 : 8-benzchromone	M. p. (*f*)	Trace	—
No. 28; 5 hours; 260°	6 : 7-Benzflavone (linear naphthaflavone) [10]	M. p. (*h*)	20	70 (*h*)
No. 29; glycerol (20 parts)	6-Phenylindano-(5′ : 6′-2 : 3)-4-pyrone [8, 11]	M. p. (*h*) [10]	50 [5]	85 (*h*)
No. 30; glycerol (20 parts)	6-(*p*-Nitrophenyl)indano-(5′ : 6′-2 : 3)-4-pyrone	M. p. (*h*) [11]	66 [5]	56 (*h*)

[1] A. S. (method 2) indicates mixed m. p. with authentic specimen prepared from the ester by application of the Baker–Venkataraman transformation and cyclization of the resulting diketone. A. S. (*a*, etc.) indicates mixed m. p. with authentic specimen prepared as described in reference (*a*, etc.) (see below). M. p. (*a*, etc.) indicates m. p. in agreement with that given in reference (*a*, etc.) (see below). [2] [5] Shows that the yield given is that of crude product before crystallization: otherwise the yield of crystallized product is given. [3] Optimum conditions of cyclization determined in a series of experiments; otherwise the yields given are not necessarily maximum. [4] The crude product (10·1 g.; m. p. 91—93°) obtained by heating *o*-benzoyloxyacetophenone (20 g.) in glycerol and pouring the reaction mixture into water was kept at 0° for 48 hours and then crystallized from ligroin (400 ml.) (see Mozingo and Adkins, *J. Amer. Chem. Soc.*, 1938, **60**, 673). The solvent when evaporated in stages to 80 ml. yielded flavone (9 g.; m. p. 97°). [6] The over-all yield (42%) obtained by Doyle *et al.* (*loc. cit.*) in the conversion of *o*-hydroxyacetophenone into flavone by the Baker–Venkataraman method, $o\text{-}C_6H_4(OH)(COMe) \longrightarrow o\text{-}C_6H_4(O\text{-}COPh)(COMe) \longrightarrow o\text{-}C_6H_4(OH)(CO\text{-}CH_2\text{-}COPh) \longrightarrow$ flavone, has now been improved to about 60% by (i) increasing the yield in the esterification as described at *B* above and (ii) using the technique of Mozingo and Adkins (*loc. cit.*) for the cyclization of *o*-hydroxydibenzoylmethane. [7] Resacetophenone dibenzoate (ester No. 7) was transformed into 2-hydroxy-4-benzoyloxydibenzoylmethane (50% crude yield) by use of solid potassium hydroxide and pyridine (see C above), and the diketone was cyclized to 7-hydroxyflavone with sulphuric acid [see reference (*c*) below, and footnote 2, Table IV]. [8] The glycerol used in this cyclization was not specially dehydrated. It contained over 98% of glycerol. [9] The glycerol reaction mixture when diluted with water was extracted with ether, and the ethereal solution was washed with water and dried (Na_2SO_4). The oil remaining on evaporation of the solvent was twice extracted with boiling water to remove phloroacetophenone and benzoic acid if present, and the residue was crystallized from glacial acetic acid (charcoal); m. p. 275° [lit. (*e*) 275°]. [10] The glycerol reaction mixture when diluted with water was extracted with ether, and the extract was washed with dilute sodium hydroxide and with water and dried (Na_2SO_4). The residue obtained on evaporation of the solvent and recrystallized from aqueous alcohol had m. p. 143° [lit. (*f*) 143°]. [10] This cyclization was carried out by Dr. N. V. Nowlan (private communication). [11] This cyclization, the first application of the new method, was effected by Slavin (M.Sc. thesis, University College,

Dublin, 1948; see Bernfield and Wheeler, *J.*, 1949, 1916). [19] These compounds were purified by extraction with chloroform and treatment of the extract as described in footnote 9.

(*a*) Doyle *et al.*, *Proc. Roy. Dublin Soc.*, 1948, **24**, 291. (*b*) Virkar, *J. Univ. Bombay*, 1942, **11**, 136. (*c*) Baker, *J.*, 1933, 1381. (*d*) Allan and Robinson, *J.*, 1924, **125**, 2192. (*e*) Robinson and Venkataraman, *J.*, 1926, 2344. (*f*) Gulati and Venkataraman, *J.*, 1936, 268. (*g*) Bhullar and Venkataraman, *J.*, 1931, 1165. (*h*) Mahal and Venkataraman, *J.*, 1934, 1767. (*i*) Anand and Venkataraman, *Proc. Indian Acad. Sci.*, 1947, **26**, 279. (*j*) Bhalla, Mahal, and Venkataraman, *J.*, 1935, 868. (*k*) Nowlan, Slavin, and Wheeler, *J.*, 1950, 340.

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usually 30 minutes and 250°. A current of dry nitrogen or coal gas was passed through the reaction vessel. The resulting mixture, while still warm, was poured into 10 volumes of cold water, and the precipitated product when sufficiently solid was recovered by filtration and crystallized. If the product did not solidify an extraction procedure (see Table IV, footnote 5, and Table V, footnotes 8, 9, and 12) was employed. It was not possible to cyclize *o*-acetoxyacetophenone (ester No. 1), resacetophenone dicinnamate (ester No. 10), or 2-(toluene-*o*-sulphonyloxy)-5-methoxyacetophenone (ester No. 18) to pyrones by the glycerol dehydration method.

Method 2. The *o*-hydroxy-diketone obtained by transformation of the corresponding ester (see section C above) was boiled with glacial acetic acid containing a few drops of hydrochloric acid, and the resulting pyrone separated by controlled addition of water (see Nowlan *et al.*, *loc. cit.*). The diketones from esters Nos. 7 and 8 were cyclized with concentrated sulphuric acid (see Table V, footnote 6, and Table IV, footnote 2).

Method 3. When resacetophenone dicinnamate (ester No. 10) and ω-methoxyresacetophenone dibenzoate (ester No. 11) were subjected to the Baker–Venkataraman transformation, spontaneous cyclization of the intermediate diketone to the corresponding pyrone occurred. Details are given below.

Preparation of 3-methylflavone by Allan–Robinson aroylation of o-hydroxypropiophenone. A mixture of *o*-hydroxypropiophenone (2 ml.), benzoic anhydride (20 g.), and potassium benzoate (4 g.) was heated under reflux (mechanical stirring) at 160—180° for 6 hours. Excess of benzoic anhydride was removed by boiling the product with 5% aqueous sodium carbonate (400 ml.) for 2 hours (see section E below). Aqueous (10%) potassium hydroxide was added to strong alkalinity in the cold, and the solid which formed on keeping at 0° was recovered by filtration. It was crystallized from light petroleum (b. p. 40—60°) and, after rejection of the oil which first separated, was obtained as colourless needles, m. p. and mixed m. p. with the product of the dehydration of *o*-benzoyloxypropiophenone in glycerol (Table IV, No. 22), 72—74°. Yield 1 g. (31%).

4-Pyrones obtained by method 3 (*spontaneous cyclization of the intermediate Baker–Venkataraman diketone; see above*). Resacetophenone dicinnamate (ester No. 10), when treated with potassium hydroxide (3·0 mols.) in pyridine as described in section C above, gave, on acidification of the reaction mixture, 7-hydroxy-2-styrylchromone (62%), m. p. 238—241° (from alcohol) (Found: C, 77·3; H, 4·6. Calc. for $C_{17}H_{12}O_3$: C, 77·3; H, 4·5%). Gulati, Seth, and Venkataraman (*J.*, 1934, 1766) give m. p. 239°.

Similarly ω-methoxyresacetophenone dibenzoate (ester No. 11) when heated under reflux with potassium carbonate and pyridine for 1 hour gave on acidification 7-hydroxy-3-methoxyflavone (32%), m. p. 233—234° (from alcohol–ethyl acetate). The m. p. was not depressed by admixture with an authentic specimen prepared by the salt–anhydride aroylation method as described by Allan and Robinson (*J.*, 1924, **125**, 2194), who give m. p. 227°.

E. *Cyclizations using Benzoic Anhydride.*—(*a*) Methods available for removing excess of aromatic acid anhydride from the product of Allan–Robinson aroylations include (i) treatment with aqueous sodium carbonate (Baker, *J.*, 1933, 1388; Baker, Flemons, and Winter, *J.*, 1949, 1562), (ii) extraction with light petroleum (Sethna and Shah, *J. Indian Chem. Soc.*, 1940, **17**, 601), and (iii) extraction with carbon disulphide (Trivedi, Sethna, and Shah, *ibid.*, 1943, **20**, 171).

A method which may be of use where sulphonation is unlikely has now been devised. It consists in dissolving the reaction product in cold concentrated sulphuric acid, and adding the solution slowly with cooling to excess of water or aqueous sodium hydroxide. The anhydride is immediately hydrolysed to the acid.

(*b*) *Preparation of 3-benzoylflavone.* A mixture of *o*-benzoyloxyacetophenone (1 g.) and benzoic anhydride (3 g.) was heated at the b. p. under an air condenser for 15 minutes. The product was dissolved in cold concentrated sulphuric acid (40 ml.), and the acid solution was added under good cooling to excess (400 ml.) of 10% aqueous sodium hydroxide. Insoluble material was recovered by filtration and dissolved in ether. The ethereal solution was extracted with 2% aqueous sodium hydroxide washed with water, and dried (Na_2SO_4). The residue remaining on removal of the solvent separated from methyl alcohol in white needles, m. p. 130—132° (yield 0·2 g.) (Found: C, 80·9; H, 4·3%; *M*, 332. $C_{22}H_{14}O_3$ requires C, 81·0; H, 4·3%; *M*, 326).

3-Benzoylflavone (1·4 g.; m. p. not depressed by addition of the product obtained from *o*-benzoyloxyacetophenone and benzoic anhydride as described in the preceding paragraph) was also prepared by heating a mixture of *o*-hydroxyacetophenone (1·8 ml.), benzoic anhydride (20 g.), and sodium benzoate (4 g.) at 180° for 6 hours (mechanical stirring). Excess of benzoic anhydride was hydrolysed by boiling the product under reflux for 2 hours with 5% aqueous sodium carbonate (200 ml.). The liquid when cold was rendered strongly alkaline with 10% aqueous sodium hydroxide, and the insoluble solid residue was recovered and recrystallized from aqueous methyl alcohol.

An improved yield of 3-benzoylflavone (2·3 g.) was obtained by replacing sodium benzoate in the above preparation by triethylamine (5 g.) (see Kuhn and Löw, *Ber.*, 1944, **77**, 202). The residue insoluble in the aqueous alkali was obtained as an oil which solidified after it had been kept at 0° for 12 hours.

(*c*) *Preparation of 7-benzoyloxy-3-benzoylflavone.* A mixture of resacetophenone dibenzoate (4 g.)

and benzoic anhydride (16 g.) was heated at the b. p. under reflux for 30 minutes in an atmosphere of nitrogen. The solid obtained on cooling was ground with sodium carbonate solution (cf. Baker, *J.*, 1933, 1388), and the supernatant liquid decanted after storage. The product, 7-benzoyloxy-3-benzoylflavone, separated from alcohol in crystals (0·8 g.) having m. p. 167°. Baker (*loc. cit.*) gives the same m. p. (Found: C, 77·3; H, 4·0. Calc. for $C_{29}H_{18}O_5$: C, 78·0; H, 4·0%). The identity of the compound was confirmed by debenzoylation with sulphuric acid to 7-hydroxy-3-benzoylflavone, m. p. 265°, by the method due to Trivedi, Sethna, and Shah (*J. Indian Chem. Soc.*, 1943, **20**, 171) who give m. p. 264—265°.

(*d*) *Preparation of* 5 : 7-*dibenzoyloxy*-3-*benzoylflavone.* A mixture of phloroacetophenone tribenzoate (1 g.) and benzoic anhydride (5 g.) was heated at the b. p. for 10 minutes in an atmosphere of nitrogen. The product obtained on cooling was extracted with ligroin in the cold to remove benzoic anhydride (cf. Sethna and Shah, *J. Indian Chem. Soc.*, 1940, **17**, 601), and the residue was crystallised from alcohol (charcoal) and ligroin. It formed colourless crystals (0·1 g.), m. p. 169° (Found: C, 76·4; H, 4·3. Calc. for $C_{36}H_{22}O_7$: C, 76·3; H, 3·9%). Trivedi, Sethna, and Shah (*loc. cit.*) give m. p. 167—168° for 5 : 7-dibenzoyloxy-3-benzoylflavone.

(*e*) *Action of benzoic anhydride on acetophenone.* A mixture of acetophenone (1 g.) and benzoic anhydride (5 g.) was heated under reflux at the b. p. for periods of from 30 minutes to 6 hours. The product did not yield dibenzoylmethane.

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University College, Dublin. [*Received, February 6th*, 1950.]

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256. *The Reductive Dissolution of Ferric Oxide in Acid. Part I. The Reductive Dissolution of Oxide Films Present on Iron.*

By M. J. Pryor and U. R. Evans.

When oxidised iron is immersed in dilute acid and the α-ferric oxide is destroyed by autoreduction the rate of destruction diminishes with an increase in film thickness, with an increase in pH, and with a decrease in temperature. The activation energy, calculated from the temperature coefficient, is about 8·5 kcals. Potential measurements show that reductive dissolution is highly polarised and that the polarisation increases with a rise in pH—which explains why the destruction is so slow at high pH values.

It has been shown (Evans, *Proc. Roy. Soc.*, 1925, *A*, **107**, 228) that, when an iron specimen showing interference tints due to an oxide film is subjected to cathodic treatment in 0·02N-hydrochloric acid, the colours undergo uniform changes, indicating a thinning of the film. It was later found (Evans, *J.*, 1930, 478) that, although tinted iron specimens dipped into 0·1M-sulphuric acid quickly lost their colour, indicating the destruction of the film, the same film, if previously stripped from the metallic basis, could be preserved in the same acid for long periods. It was suggested that the rapid destruction of the films, when in electrical contact with the iron, was due to local cells, Fe (anode) | Acid | Fe_2O_3 (cathode), set up at discontinuities in the film; the ferric oxide suffers cathodic reduction and ferrous ions pass into the liquid. This conclusion is supported by the observations (Evans, *J.*, 1930, 481) that the destruction of the films on tinted iron by 0·01M-sulphuric acid can be prevented by the application of a sufficient anodic current, whereas a cathodic current accelerates their disappearance, and that the destruction of the colours can be prevented by the presence of an oxidising agent in sufficient concentration (0·1M-chromic acid in 0·01N-sulphuric acid). Evidently the disappearance of the films is due to a combination of reduction and dissolution.

In earlier papers the rapid destruction of oxide films on cathodic areas was called "cathodic reduction" or "reductive dissolution." In the present paper the reductive dissolution occurring in a short-circuited cell Fe | Acid | Fe_2O_3 will be called "autoreduction," the term "cathodic reduction" being restricted to destruction brought about by an external E.M.F.

Cathodic reduction has been applied to the determination of the thickness of oxide films on iron (Miley, *Carnegie Schol. Mem. Iron & Steel Inst.*, 1936, **25**, 197; Evans and Miley, *Nature*, 1937, **139**, 283; Miley and Evans, *J.*, 1937, 1295). The oxidised specimen is made the cathode under a constant current in ammonium chloride solution, where the pH is too high to permit autoreduction. The weight of film destroyed can be calculated from the number of coulombs needed—provided that no alternative cathodic reaction proceeds simultaneously.

Despite much work on the application of cathodic reduction, no adequate account of the mechanism has been offered. The earlier papers suggested a reduction of ferric to ferrous oxide which was believed to dissolve instantaneously in the electrolyte; but Hoar (private

communication) has argued that there is no reason why *massive* ferrous oxide should dissolve with great speed.

The present paper describes an attempt to obtain fuller information regarding the autoreduction and cathodic reduction of films on heat-tinted iron immersed in electrolytes containing dissolved oxygen; it includes studies of the influence of film thickness, pH, temperature, and the presence of complex-forming ions on the rate of reductive dissolution.

Experimental.

Materials.—The iron used in these experiments was in the form of annealed sheet, 0·02 cm. thick; it was kindly supplied by the British Iron and Steel Research Association; analysis showed: C, 0·005; Si, 0·0075; S, 0·013; P, 0·003; Mn, 0·007; Ni, 0·018; Cr, 0·02; Cu, 0·003; O, 0·12; N, 0·008; H, 0·00009%. The chemicals were of AnalaR quality.

Each specimen was degreased thoroughly in xylene, abraded with 3/0 emery paper, swabbed with acetone, and dried with filter-paper. Except in experiments designed to show the effect of film thickness on the rate of autoreduction, the specimens were tinted in the air-oven at 210° for 30 hours, in order to obtain an oxide film showing the first-order red-brown interference colour. This particular colour was chosen because Constable (*Proc. Roy. Soc.*, 1929, *A*, **125**, 378) had shown it to be obtained only over a fairly narrow range of film thickness.

A disc of iron of the same composition, measuring 2 cm. in diameter and 0·1 cm. thick, was treated in an identical manner, and its surface examined by electron diffraction, the reflection method being used, in order to determine the structure of the heat-tinted film; this examination was kindly carried out by Mr. J. W. Menter. The values of the spacings, based on gold-leaf as a standard, are shown in the following table. They are in good accord with those previously obtained from α-ferric oxide by

Ring radius (cm.).	Spacing (A.).	Intensity.	A.S.T.M. *X*-ray spacings for α-Fe_2O_3.	A.S.T.M. *X*-ray intensity.	*hkl*.	Ring radius (cm.).	Spacing (A.).	Intensity.	A.S.T.M. *X*-ray spacings for α-Fe_2O_3.	A.S.T.M. *X*-ray intensity.	*hkl*.
0·86	3·80	W	3·68	0·18	11·0	1·89	1·73	M	1·69	0·63	321
1·19	2·74	V.S.	2·69	1·00	21·1	2·16	1·51	V.S.	1·485	0·50	310
1·29	2·53	V.S.	2·51	0·75	10·1	2·20	1·47	V.S.	1·454	0·50	211
1·45	2·19	M	2·20	0·18	20·2	2·39	1·365	W	1·381	0·03	433
1·76	1·86	S	1·84	0·63	22·0	2·66	1·23	V.W.	1·26	0·13	202

V.S. = very strong. S = strong. M = moderately strong. W = weak. V.W. = very weak.

X-ray diffraction ("Index of *X*-Ray Diffraction Constants," A.S.T.M., 1945) and suggest that the film responsible for the first-order colour is largely composed of rhombohedral α-ferric oxide.

Experimental Method.—It was observed during preliminary experiments that specimens tinted to first-order colours changed their tints uniformly when exposed to 0·1*N*-hydrochloric acid. Furthermore, the period needed for the disappearance of colour was independent of the area of specimen exposed to the acid; after the colour had vanished, the specimen almost certainly still carried an invisible oxide layer. The boundary between the visible and invisible films, however, represented a convenient, if arbitrary, end-point.

This "boundary method" showed good reproducibility as regards the period of immersion necessary for the autoreduction of first-order oxide films. A portion of the specimen was exposed to the acid until the visible films had disappeared; the specimen was then immersed more fully and the time required for the disappearance of the boundary between the visible and the invisible film noted. The scatter was generally less than 10%, except where the film was destroyed very quickly.

The Effect of Film Thickness.—Pure iron specimens measuring 6 × 2 cm. and 0·02 cm. thick, abraded and degreased as previously described, were heated in the air-oven at 300° for different times to give oxide films of the following interference colours:

Interference colour.	Approx. thickness (A.) (Evans and Miley, *Nature*, 1937, **139**, 283).	Time for autoreduction (secs.).
1st-Order straw	440	2—3
1st-Order red-brown	560	5—5
1st-Order violet	695	7—10
Silvery hiatus (light blue)	725	300

The times taken for the autoreduction of these films in 0·1*N*-hydrochloric acid (pH = 1·12) at constant temperature (20·5°) were determined by using the "boundary method".

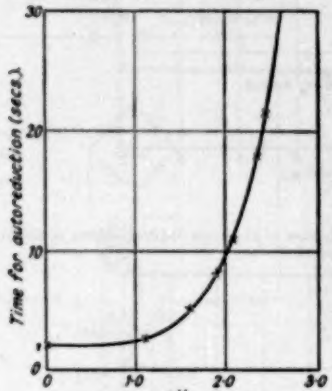
The first-order straw, red-brown, and violet films all thinned rapidly and apparently uniformly during autoreduction, disappeared sharply after a definite period of immersion (see above table), and left a clean metal surface. With films of the "silvery hiatus," autoreduction spread outward from certain points so that the destruction of the film was non-uniform; indeed, the whole range of first-order interference colours could be observed simultaneously on specimens immersed for 30 seconds; even after 300 seconds the films had not completely disappeared. These thicker films are known to be duplex (Evans, Iron and Steel Inst. Special Rep., 1938, **21**, 225), with a lower layer of magnetite next to the metal; when subjected to autoreduction they left behind a black residue which was extremely resistant to reductive dissolution. If the specimen remained in the solution for a further hour, the black film was undermined, leaving a clean metal surface. The film, which remained suspended in the solution, was highly magnetic.

These results were confirmed by a different method. If the specimen was electropolished, in the perchloric acid–acetic acid bath developed by Jacquet (*Compt. rend.*, 1948, **227**, 556), before being heat-tinted, the interference colours showed very distinctly under the microscope. It was observed that the colours differed from grain to grain and that a film which appeared red-brown to the naked eye was, in fact, composed of different grains showing such interference colours as blue, violet, red-brown, and straw, when examined under the microscope. Even light straw specimens contained a few violet and blue grains and the proportion of grains showing these colours increased with the mean film thickness. This variation of oxide thickness from grain to grain is doubtless due to the fact, pointed out by Mehl and McCandless (*Trans. Amer. Inst. Min. Met. Eng.*, 1937, **125**, 531), that the rate of growth of oxide films on iron is anisotropic.

An electropolished iron specimen, measuring 4 × 2 cm. and 0·02 cm. thick, was therefore gradient-tinted in a Bunsen flame, half-immersed lengthways in 0·1*N*-hydrochloric acid for 20 seconds, washed rapidly in distilled water, and dried on filter-paper. There was a shift in the colours, relative to the original tints, which were preserved unchanged above the water-line—similar to that obtained previously with an external current (Evans, *Proc. Roy. Soc.*, 1925, *A*, **107**, 228). A comparison with the original colours, at a magnification of 400, showed that the original first-order straw and red-brown regions were almost completely decolorised, with the exception of isolated grains carrying blue interference films. Evidently the blue film was more resistant to reductive dissolution than thinner films. In the first-order violet range original red-brown and straw colours were largely reduced, many grains carrying violet

FIG. 1.

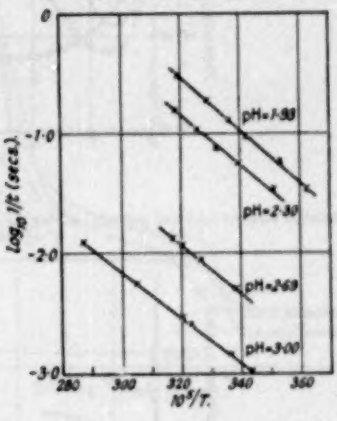
Relation between pH and the time of auto-reduction of first-order red-brown films.



First-order red-brown films. Temp. = 20·5°.

FIG. 2.

Relation between the logarithm of the inverse of the time of autoreduction and the inverse of the absolute temperature.



films were thinned and after short-time treatments appeared red-brown or straw, but the blue colours were mostly unchanged. The silvery film appeared to be composed of approximately equal proportions of grains showing second-order yellow and first-order blue tints. Film reduction in 20 seconds was so incomplete that the contrast at the " water-line " was much less sharp than in the first-order violet, red-brown, and straw ranges.

The Effect of Hydrogen-ion Concentration.—The effect of pH on the autoreduction of first-order red-brown α-ferric oxide films on specimens measuring 7 × 2·5 × 0·02 cm. was determined by the boundary method in eight solutions of potassium chloride and hydrochloric acid of molar chloride-ion concentration covering the pH range 0·02—5·09; all experiments were carried out in 50 ml. of solution held at constant temperature (20·5°) in a water-bath and were repeated at least six times with fresh solutions; Fig. 1 is based on the average of results obtained.

When the pH of the solution exceeded 3·0, autoreduction of the film was not observed even when the specimen was left in the solution for 24 hours. Portions of the film, however, had been undermined, probably by an extension of anodic areas on the specimen, and could be observed in suspension in the solution. Under the microscope (× 500) these fragments of film exhibited abrasion marks probably inherited from the iron. The remaining film on the specimens showed its original red-brown colour.

The Effect of Temperature.—The relation between time of autoreduction and temperature was determined by the same procedure for first-order red-brown films in four of the above potassium chloride–hydrochloric acid solutions having pH values of 1·93, 2·30, 2·69, and 3·00. The solutions were kept at the appropriate temperature in a water-bath, each determination being carried out at least six times in fresh solutions; the rate of autoreduction increased with a rise in temperature and when the logarithm

of the inverse of the time was plotted against the inverse of the absolute temperature, a family of parallel straight lines was obtained (Fig. 2).

Potential Measurements during Autoreduction.—Two series of experiments were carried out in which potential measurements were taken during autoreduction of visible oxide films on heat-tinted specimens.

FIG. 3.

Relation between time and potential during the autoreduction of films of different thickness at pH = 2·37 and at 17·5°.

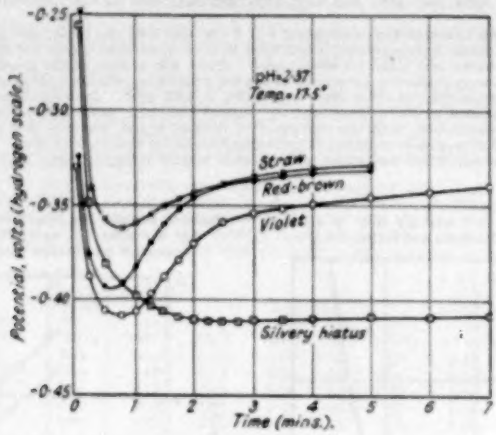
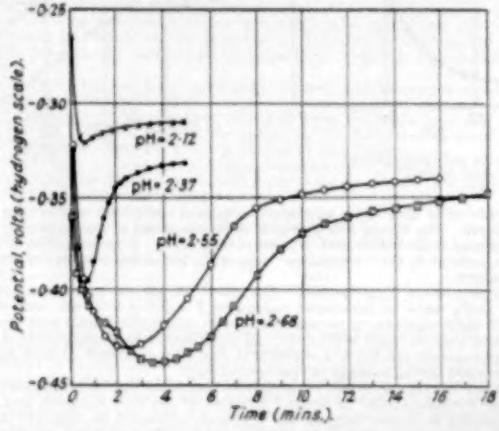


FIG. 4.

Relation between time and potential during the autoreduction of first-order red-brown films in solutions of different pH at 17·5°.



The potential was measured against a silver–silver chloride electrode enclosed in a tubulus drawn out to a tip of 0·1 cm. internal diameter. The specimen was mounted on a fibre frame (Evans, *J. Soc. Chem. Ind.*, 1928, **47**, 731), so that an area measuring 3·5 × 2·5 cm. was immersed in the electrolyte, the tip of the tubulus being situated 0·1 cm. away from the iron; in these experiments a large volume (400 ml.) of solution was used. The variation of potential difference with time was measured by means of a valve potentiometer.

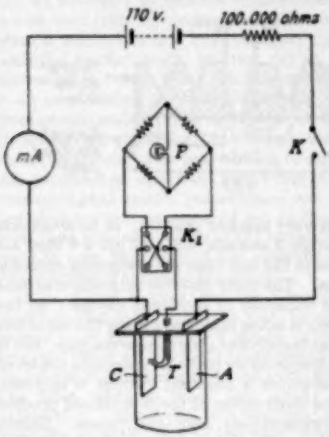
In the first series of experiments the influence of film thickness on the shape of the potential–time curves was investigated. The solution used (pH = 2·37) was maintained at 17·5° and had N-chloride-ion concentration. The specimens were tinted to straw, red-brown, violet, and silvery hiatus colours, experiments being conducted in triplicate. Typical curves relating the potential, on the standard hydrogen scale, to time are shown in Fig. 3.

In the second series the influence of the pH of solutions of N-chloride-ion concentration, at constant film-thickness (first-order red-brown) and temperature (17·5°), on the form of the potential–time curves was investigated. The range of pH covered by the solutions was 2·12—2·68. Experiments were again in triplicate and typical curves are shown in Fig. 4.

Potential Measurements during Cathodic Reduction.—Single electrode-potential determinations were carried out during cathodic reduction in 0·1N-ammonium chloride solution (pH = 4·94), containing dissolved oxygen, an electrical circuit being used similar to that of Miley (*Carnegie Schol. Mem. Iron and Steel Inst.*, 1936, **25**, 197), except that the single-electrode potential of the cathode was measured against a silver–silver chloride electrode (Fig. 5). The electrodes were iron sheets of standard size, one of which (the cathode) had been tinted to the required interference colour, whilst the other (the anode) had been freshly abraded with 3/0 emery paper. The electrodes were mounted on a fibre frame so that they were 3·5 cm. apart. A tubulus, drawn down to 0·1 cm. internal diameter, was also mounted on the frame so that its tip was situated 0·1 cm. distant from the heat-tinted cathode. 250 Ml. of 0·1N-ammonium chloride solution were used in each experiment, the electrodes being immersed to a depth of 2·5 cm.

FIG. 5.

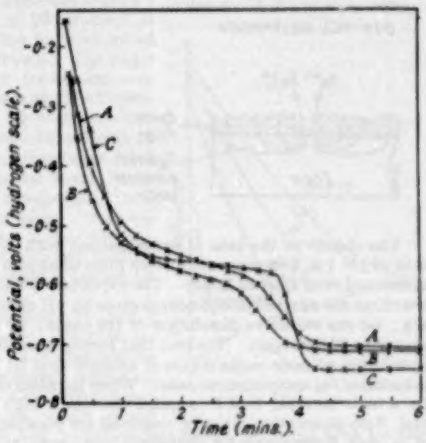
Circuit used for the cathodic reduction of oxide films.



C = *Cathode*. *A* = *Anode*. *T* = *Tubulus*. *K* and K_1 = *Keys*. *P* = *Valve potentiometer*. *mA* = *Sensitive milliammeter*.

FIG. 6.

Potential–time curves for first-order violet films.



A, *B* = *In* 0·1N-NH_4Cl.
C = *In* 0·1N-NH_4Cl + KCN (0·7 *g./l.*).

Typical potential–time curves for first-order violet films are shown in Fig. 6, curves *A* and *B*. Curve *C* was obtained with an addition of 0·7 g./l. of potassium cyanide, which raised the initial pH of the electrolyte from 4·94 to 5·05. Similar curves were obtained with oxide films of different thickness. The alteration produced by cyanide addition was also obtained with films of different thickness.

DISCUSSION.

During autoreduction the anodic areas are provided by iron exposed to the acid at discontinuities in the oxide film. The electrons, liberated by the anodic reaction, will pass from the metal, through the oxide film, and take part in the cathodic reaction at the oxide–solution interface. Consequently, one of the factors controlling the rate of reductive dissolution will be the electronic conductivity of the film.

The fact that the specimen carrying thin first-order films changes colour uniformly during autoreduction suggests that these films possess sufficient electronic conductivity to permit the rapid, uniform, conduction of electrons.

The bulk conductivity of ferric oxide is, however, known to be low (Somerville, *Chem. Met. Eng.*, 1912, **10**, 423). In the films of hiatus and second-order thickness the area of iron exposed

at cracks is much smaller, particularly as a magnetite layer exists below the α-ferric oxide. Their greater thickness imposes a greater resistance to the passage of electrons, and since it has been shown by Bevan, Shelton, and Anderson (*J.*, 1948, 1729) that electrons often move more readily over the surface of semi-conducting oxides than through the lattice, it is probable that such reductive dissolution as occurs will take place at or near to discontinuities or at places where the film is abnormally thin. This may explain the slow and irregular form of autoreduction observed on these thicker films. The difference between the behaviour of thin and thick films is illustrated diagrammatically in Figs. 7(*a*) and (*b*), in which, for simplicity, the metal surface is assumed to be planar.

The rate of autoreduction was shown to increase rapidly with increasing temperature. If it is assumed that the time for autoreduction is inversely proportional to the mean rate of autoreduction, then the activation energy can be calculated from the gradient of the parallel family of straight lines in Fig. 2. The value calculated, 8·5 kcals./g.-mol., may be useful later in deciding the rate-determining step during reductive dissolution.

FIG. 7 (*a*).

Electrons liberated at an anodic area passing uniformly through a thin oxide film.

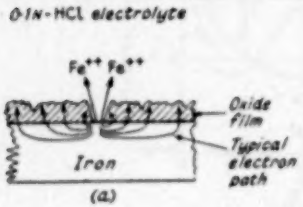
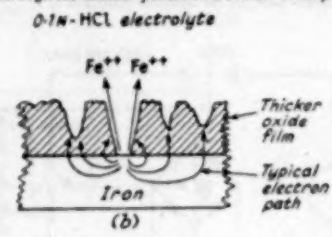


FIG. 7 (*b*).

Electrons liberated at an anodic area passing preferentially through the thinner points in a thicker oxide film.



The change in the rate of autoreduction with pH is very marked (Fig. 1); in hydrochloric acid of pH 1·0, first-order red-brown films disappear within 2 seconds, while at pH 4·0 they are unthinned even after 24 hours. The explanation may lie in the fact that the competing cathodic reactions are affected in different degrees by pH changes. The three possible cathodic reactions are: (*a*) the reductive dissolution of the oxide; (*b*) the reduction of dissolved oxygen; (*c*) the evolution of hydrogen. The fact that hydrogen evolution is never observed during the reductive dissolution of ferric oxide makes it unlikely that (*c*) is an important alternative reaction, but it is included for completeness' sake. When the films are destroyed by cathodic reduction achieved by a high external E.M.F. applied through a high resistance, a constant current is imposed, and, if no alternative cathodic reactions are possible, the destruction of the film should proceed at a rate determined by Faraday's law, even at comparatively high pH values. During autoreduction, however, the current does not necessarily remain constant, but is determined by polarisation and possibly resistance. Thus if the reductive dissolution of ferric oxide is highly polarised, the current devoted to oxide reduction will diminish and consequently the rate of film destruction must become slower.

Of the three possible cathodic reactions, (*b*) and (*c*) may be represented by the equations

$$O_2 + 4H^+ + 4e = 2H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$2H^+ + 2e = H_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The work of Miley and Evans (*J.*, 1937, 1295) leads to the conclusion that a molecule of ferric oxide requires two electrons for reductive dissolution. Since all the iron found in solution is in the ferrous condition, the reductive dissolution of ferric oxide may be represented by the equation

$$Fe_2O_3 + 6H^+ + 2e = 2Fe^{++} + 3H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

This reaction undoubtedly takes place in steps but the value of the equilibrium potential will be independent of the mechanism.

The anodic reaction

$$Fe - 2e = Fe^{++} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

is not directly affected by pH. The unpolarised single-electrode potentials of the three possible cathodic reactions will be influenced respectively by pH according to the relationships

$$(1)\ E = E_0 + (RT/F)\log_e [H^+]$$
$$(2)\ E = E_0 + (RT/F)\log_e [H^+]$$
$$(3)\ E = E_0 + (3RT/F)\log_e [H^+]$$

all other products being assumed to be in the standard state. Thus the unpolarised electrode potential of the third reaction (the reductive dissolution of oxide) is affected by pH three times as strongly as the other two reactions.

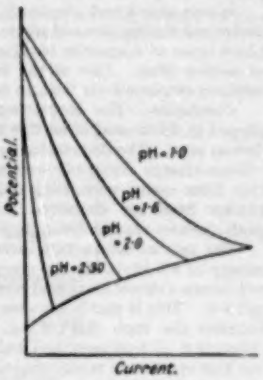
In practise, few reactions take place rapidly near their equilibrium potentials and so it becomes necessary to consider the effect of pH on polarisation. The unpolarised potential of the reductive dissolution is given by the equation

$$(3A)\ E = E_0 + (RT/2F)\log_e [H^+]^6/[Fe^{++}]^2$$

[of which (3) is a special case corresponding to normal activity of ferrous ions]. The value of E_0 calculated from the thermodynamic data of Camps (*J. New Eng. Waterworks Assoc.*, 1946, **60**, 188) and Bichowsky and Rossini ("The Thermochemistry of Chemical Substances," 1936, p. 89, Reinhold Publishing Co.) is +1·035 volts. The unpolarised electrode potential at pH 4·0 and an arbitrary ferrous-ion concentration of 10^{-4} g.-ion/l. is +0·68 volt (this represents the concentration to be expected when a red-brown film has been half destroyed). The single potential of the anodic reaction (4) at this ferrous-ion concentration is −0·62 volt. Thus it can be seen at pH 4·0 there is an open-circuit potential difference of 1·3 volts between these anodic and cathodic reactions. In several determinations of the rate of autoreduction multiple scratch lines were ruled on the specimens after heat-tinting to expose the metal; since this produced no alteration in the rate of autoreduction, it was concluded that anodic polarisation was not high. Thus the fact that autoreduction could not be detected at this pH suggests that the polarisation of the reductive dissolution of ferric oxide is very high so that the cathodic current is carried by the alternative cathodic reactions.

FIG. 8.

Probable effect of pH on the reductive dissolution of ferric oxide.



Figs. 3 and 4 show that the compromise potential during autoreduction falls rapidly at first, flattens out, and then increases to an approximately steady value. (The compromise potential obtained in a highly conducting electrolyte represents the intersection of the anodic and cathodic polarisation curves.) The time taken to reach this steady value, which is the potential of "film-free" iron evolving hydrogen, approximates to the predicted time for the complete autoreduction of the film. During hydrogen evolution it has been suggested (Gatty and Spooner, "The Electrode Potential Behaviour of Corroding Metals," 1938, p. 253, Clarendon Press) that practically the whole metallic surface is covered with hydrogen, with anodic attack taking place at isolated points which do not remain stationary. This will result in comparatively low cathodic and high anodic polarisation, which may explain why the compromise potential during the hydrogen evolution type of corrosion is higher than during autoreduction. The low values of the compromise potential (between −0·32 and −0·45 volt) during autoreduction are consistent with high polarisation of the cathodic reaction (E_0 = +1·035 volts) and low polarisation of the anodic reaction (E_0 = −0·44 volt). Furthermore it can be seen from Fig. 4 that the minimum value of the compromise potential decreases from −0·32 volt to −0·44 volt as the pH of the solution increases from 2·12 to 2·68. Since the anodic reaction is not directly influenced by pH, and since a change in pH from 2·12 to 2·68 would change the unpolarised potential of reductive dissolution by only 49 mv., it follows that the polarisation of this reaction increases with an increase in pH; this is illustrated diagrammatically in Fig. 8. Consequently, the alternative cathodic reactions will increase in importance as the pH rises. This will be discussed more fully in Part II.

Fig. 3 shows that the width of the "well" in the potential–time curves increases with film thickness, at constant pH—a fact which accords with the view that the time taken to reach the steady value of potential is that required for the autoreduction of the oxide film. The

potentials of specimens carrying silvery hiatus films, however, did not rise to that of a " film-free " specimen immersed in the same electrolyte, but remained at a value of −0·42 volt, *i.e.*, approximately 0·1 volt more negative. This can be explained by the circumstance that the subsequent cathodic reaction probably now occurs at the surface of the unreduced magnetite, the distribution of which may determine the ratio of anodic to cathodic areas and consequently the relative values of the anodic and cathodic polarisations.

The arguments just set forth offer a satisfactory explanation of the remarkable effect of pH on the rate of destruction of the films.

The results of some single-electrode potential measurements carried out during the cathodic reduction of first-order violet films in 0·1*N*-ammonium chloride solution containing dissolved oxygen are shown in Fig. 6. The potential falls, rapidly at first, and then flattens out. This is followed by a second sharp drop to the potential of hydrogen evolution. The second drop was considered by Miley to mark the point at which the oxide reduction was complete. The addition of a small quantity of potassium cyanide, which forms soluble complexes with ferrous ions, raises the potential during reductive dissolution and emphasises the sharpness of the second drop (curve *C*, Fig. 6). This is in accordance with equation (3A) which indicates that the single-electrode potential could be raised by decreasing the concentration of ferrous ions. The low values of potential observed during reductive dissolution (−0·5 to −0·6 volt) provide further evidence that this reaction is highly polarised, since the unpolarised electrode potential at pH 5·0 and a ferrous-ion concentration of 10^{-4} g.-ion/l. is +0·504 volt.

It was mentioned previously that the magnetite layer present in the thicker films was not destroyed during autoreduction. During the determinations of single-electrode potentials a black layer of magnetite invariably remained on the specimens after the reductive dissolution of duplex films. One of the features of electrometric determinations of film thickness—as hitherto employed—is that, in testing duplex films, only the ferric oxide layer is estimated.

Conclusion.—The destruction of ferric oxide films which occurs when heat-tinted iron is dipped in dilute acid is *not* due to *direct* dissolution as *ferric* ions, but to *reductive* dissolution as *ferrous* ions. The destruction occurs quickly and regularly when the films are thin, so that the colours change uniformly over the whole surface; probably electrons can pass through these thin films easily, permitting uniform cathodic action at all points of the outer surface. The thicker films are destroyed slowly and irregularly, probably because the reaction occurs preferentially around discontinuities.

The rate of destruction increases with temperature, and the results suggest an activation energy of 8·5 kcals. for the controlling stage. The effect of pH is remarkable; the first-order red-brown colours disappear within 2 seconds at pH 1·0, but are unchanged after 24 hours at pH 4·0. This is partly because the equilibrium potential of the reductive dissolution reaction includes the term $(3\boldsymbol{R}T/\boldsymbol{F})\log_e[H^+]$, whereas the values for the two alternative reactions (liberation of hydrogen and reduction of oxygen) include the term $(\boldsymbol{R}T/\boldsymbol{F})\log_e[H^+]$, so that the first reaction is more influenced by rise in pH than the other two; an even more important reason is that the first reaction is subject to high polarisation which increases with a rise in pH.

The authors are indebted to Mr. J. W. Menter for carrying out the electron-diffraction examination and to Dr. J. E. O. Mayne for valuable discussion. One of the authors (M. J. P.) wishes to thank the Department of Scientific and Industrial Research for financial assistance.

Department of Metallurgy, University of Cambridge. [*Received, December 15th*, 1949.]

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257. *The Reductive Dissolution of Ferric Oxide in Acid. Part II. The Reductive Dissolution of Powdered Ferric Oxide.*

By M. J. Pryor and U. R. Evans.

Experiment shows that both the rate and the current efficiency of reductive dissolution of α-ferric oxide powders diminish with an increase in the temperature of previous ignition, with an increase in the time of reduction, and with an increase in pH of the electrolyte. It is concluded that, at pH values below 2·0, the rate of reductive dissolution is controlled by surface conductivity of the oxide and hence by the number of surface defects. When the electrolyte is de-aerated the current efficiency greatly increases, although the rate of reductive dissolution is not significantly changed. Evidently, the rôle of dissolved oxygen as a cathodic depolariser is most pronounced at low current densities.

The study of the reductive dissolution of films of α-ferric oxide present on iron, described in Part I (preceding paper), was complicated by the facts that: (1) any attempt to grow films

thicker than about 700 A. was accompanied by the formation of a layer of magnetite next to the metal; (2) thin films of α-ferric oxide were probably in a strained condition when in contact with the iron. Consequently, an attempt was made to study the reductive dissolution of powdered samples of α-ferric oxide, prepared by ignition of the precipitated, hydrated oxide.

Since the bulk conductivity of this oxide is low (Bevan, Shelton, and Anderson, *J.*, 1948, 1729), considerable difficulty was encountered in developing a suitable form of cathode. The one used eventually consisted of a fixed mass of oxide floating on a pool of redistilled mercury; electrical contact to this electrode was made by means of a shielded platinum wire dipped into the mercury.

By using this electrode in conjunction with a sheet iron anode, the influence of the temperature of ignition of the oxide, its surface condition, the pH of the electrolyte, and the presence of different acids on the rate of autoreduction was determined. The current flowing in the cell was measured continuously throughout the experiments so that the current efficiency of the oxide reduction could be calculated.

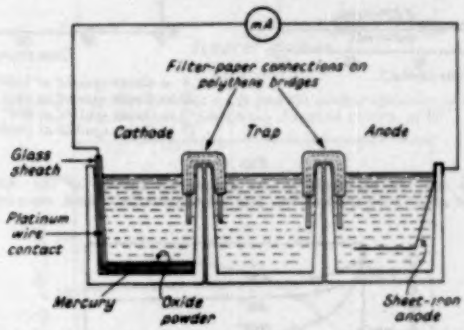
The experiments mentioned above were carried out in electrolytes containing dissolved oxygen. The cell, however, was suitable for experiments under anærobic conditions since the autoreduction of oxide powders was much slower than that of oxide films. Many of the previous experiments were repeated under anærobic conditions in order to study the rôle of oxygen as a cathodic depolariser.

Experimental.

Materials.—The oxides under examination were prepared by precipitating a boiling acidified solution of ferric ammonium sulphate with ammonia, and igniting the precipitate at different temperatures

Fig. 1.

The mercury cell.



varying between 200° and 1000°. The oxides ignited above 300° consisted of rhombohedral α-ferric oxides (*Sm*), but those ignited below 300° were amorphous to *X*-rays. Full details of the preparation and *X*-ray examination of these oxides have been recorded by the authors (*J.*, 1949, 3330).

The iron anodes were cut from a sheet, 0·02 cm. thick, of the same composition as that used in Part I. All chemicals were of "AnalaR" quality.

The Mercury Cell.—The mercury cell (Fig. 1) consisted of three compartments, each being a square glass vessel, measuring approximately 4 × 4 × 4 cm., and holding about 60 ml. of solution. The cathode compartment contained 50 ml. of electrolyte together with 0·25 g. of the oxide under examination floating on a pool of redistilled mercury, which was chosen mainly on account of its high overpotential of hydrogen evolution. Electrical connection to the mercury was secured by a platinum wire shielded from direct contact with the electrolyte by a glass tube. The anode compartment contained a sheet of iron, the edges of which were screened with several coats of polystyrene lacquer, leaving an area of 1 sq. in. exposed to the electrolyte. The two compartments were connected together by means of filter-paper strips carried on small bridges made from polythene, through a central compartment which acts as a trap, to prevent mixing of the respective solutions. The edges of the vessels in contact were smeared with vaseline to prevent "siphoning away" of the electrolyte. The cell could be short-circuited by joining the platinum wire contact to the iron anode through a switchboard and sensitive milliameter. Measurements of the electrode potential of the anode, and of the potential differences across the cell were made by means of a valve potentiometer and a silver–silver chloride electrode. Experiments were carried out with the cell contained in an asbestos-lined steel box, placed inside a room thermostatically controlled at 25° ± 0·25°.

Characteristics of the Cell.—The current was found to diminish with time; reproducible results were

only obtained after special precautions had been taken to exclude vibrations. Typical current–time curves obtained with different acids containing dissolved oxygen in the cell

Mercury (cathode)|Acid||Iron (anode)

are shown in Fig. 2. The potential difference–time curves had exactly the same form as the current–time curves. The ohmic resistance of the cell, calculated from the ratio of potential difference to current, varied between 105 ohms in 1·0N-solutions of hydrochloric, sulphuric, or perchloric acid, and

FIG. 2.

Currents generated by the cell Hg|*Acid*|Fe *at 25°.*

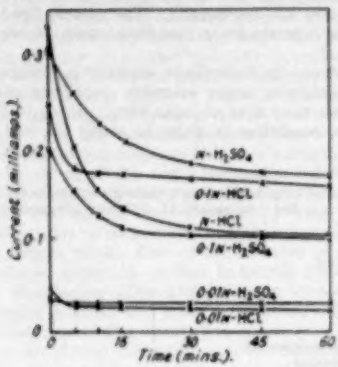
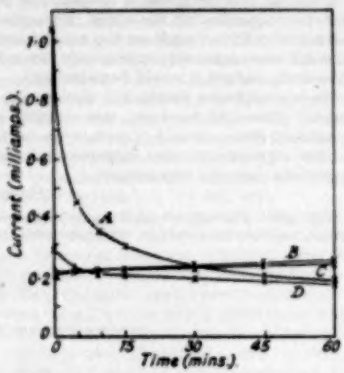


FIG. 3.

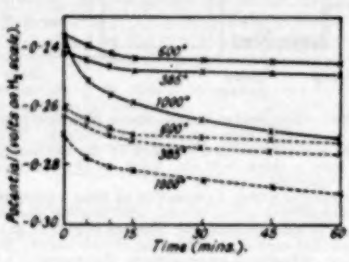
Currents generated by the cell Fe_3O_4,Hg|*Acid*|Fe *at 25°.*



A = *Oxide ignited at* 1000° *in* 1·0N-HCl.
B = *Oxide ignited at* 385° *in* 0·1N-HCl.
C = *Oxide ignited at* 600° *in* 0·1N-HCl.
D = *Oxide ignited at* 1000° *in* 0·1N-HCl.

FIG. 4.

Relation between time and the potentials of the anode and cathode of the cell Fe_3O_4,Hg|*Acid*|Fe *using oxide ignited at different temperatures and* 0·1N*-hydrochloric acid, containing dissolved oxygen at* 25°.



×——× *Potential of cathode.*
×- - - - × *Potential of anode.*

140 ohms in 0·01N-solutions of the same acids. As the resistance of the valve potentiometer was of the order of 10^8 ohms, it could divert only a negligible fraction of the total current from the milliameter. The actual values of the electrode potentials of the anode and cathode, in 0·1N-hydrochloric acid, were measured against a standard silver–silver chloride electrode. The lowest potential reached by the cathode was −0·28 volt.

When 0·25 g. of the oxide ignited at 1000° was placed in the cathode compartment, the initial value of the current was usually slightly higher (Fig. 3) in 0·1N-acids and many times larger in 1·0N-acids. The initial current usually diminished within 15 minutes, to nearly the same value as that obtained in the absence of oxide. The ratio of potential difference to current was approximately constant and

gave a value of 110—130 ohms for the resistance of the cell Fe_xO_y, Hg (cathode)|Acid|Fe (anode). The actual values of the anodic and cathodic potentials are shown in Fig. 4.

With oxides ignited at 600° and below, the initial current in 0·1N-hydrochloric acid was approximately 0·22 milliamp., and increased steadily throughout the period of the experiment (curves *B* and *C* in Fig. 3). The ratio of potential difference to current remained constant, giving a value of 120 ohms for the resistance of the cell containing the oxide ignited at 385°. Measurements of the anodic and cathodic potentials (Fig. 4) showed that, although both fell with time, the potential of the anode decreased more rapidly than that of the cathode. This is in direct contrast to the oxides ignited at 700° and above.

FIG. 5.

Relation between temperature of ignition and the percentage reductive dissolution, in one hour, of ferric oxide in 0·1N-hydrochloric acid, containing dissolved oxygen, at 25°.

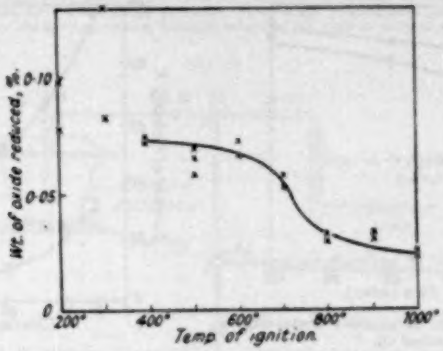
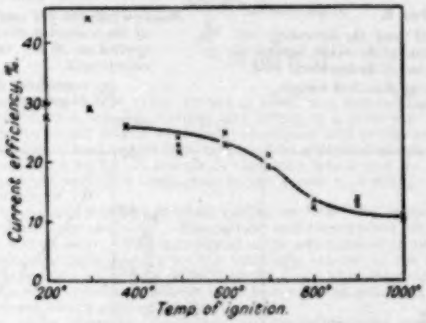


FIG. 6.

Relation between temperature of ignition of ferric oxide and the current efficiency of reductive dissolution in 0·1N-hydrochloric acid, containing dissolved oxygen, at 25°.



Procedure.—0·250 G. of the oxide under examination was carefully weighed out and introduced into the cathode compartment in the manner described by Pryor and Evans (*loc. cit.*). During the experiments, the variation of current, anodic potential, and potential difference across the cell, with time, was measured. At the end of the experiment the solution in the cathodic compartment was filtered rapidly, under reduced pressure, through three layers of Whatman No. 42 filter-paper, and iron determined colorimetrically by the thioglycollic acid method (Swank and Mellon, *Ind. Eng. Chem. Anal.*, 1938, **30**, 7). The quantity of oxide dissolved directly during the period of the experiment was derived from blank readings obtained in the absence of a cathodic current. This correction was subtracted from the total iron content of the solution in the cathodic compartment; the balance was expressed as the percentage by weight of oxide reductively dissolved.

The number of coulombs flowing during the experiment was estimated by Simpson's rule and the percentage efficiency of the reductive dissolution calculated.

Results in the Presence of Oxygen.—The manner in which the weight percentage of oxide reductively dissolved by one hour's treatment with 0·1N-hydrochloric acid, varied with the temperature of ignition

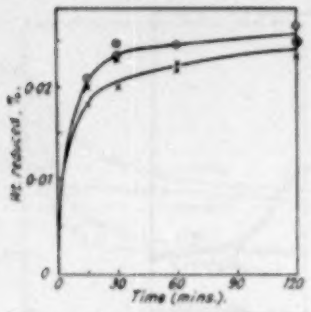
of the oxide is shown in Fig. 5; the relation between cathodic efficiency and temperature of ignition is illustrated in Fig. 6. The results obtained with oxide, ignited at temperatures of 300° and below, are probably not reliable owing to the comparatively high rate of direct dissolution in 0·1*N*-acid.

FIG. 7.

Relation between time and the percentage reductive dissolution of the oxide ignited at 1000° in 0·1N-hydrochloric acid

(a) *containing dissolved oxygen,*
(b) *de-aerated*

at 25°.



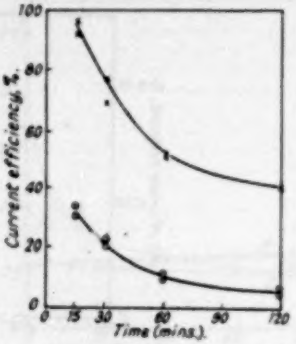
○——○ *Results in solutions containing dissolved* O_2.
×——× *Results in de-aerated solutions.*

FIG. 8.

Relation between time and the current efficiency of the reductive dissolution of the oxide ignited at 1000° in 0·1N-hydrochloric acid

(a) *containing dissolved oxygen,*
(b) *de-aerated*

at 25°.



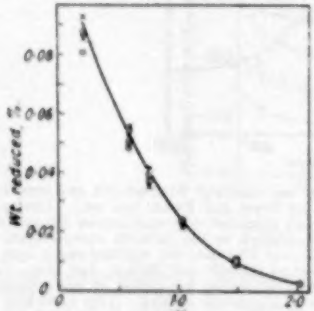
○——○ *Results in solutions containing dissolved* O_2.
×——× *Results in de-aerated solutions.*

FIG. 9.

Relation between pH and the percentage reductive dissolution of the oxide, ignited at 1000°, in solutions of hyarochloric acid

(a) *containing dissolved oxygen,*
(b) *de-aerated*

at 25°.



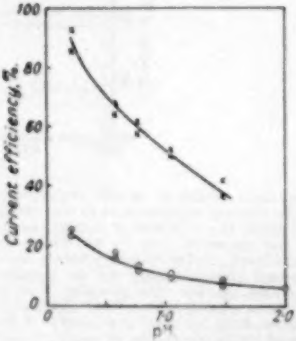
○ *Results obtained in solutions containing dissolved* O_2.
× *Results obtained in de-aerated solutions.*

FIG. 10.

Relation between pH and the current efficiency of the reductive dissolution of the oxide, ignited at 1000°, in solutions of hydrochloric acid

(a) *containing dissolved oxygen,*
(b) *de-aerated*

at 25°.



○——○ *Results obtained in solutions containing dissolved* O_2.
×——× *Results obtained in de-aerated solutions.*

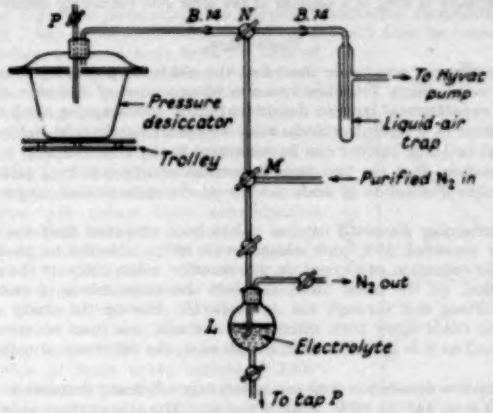
The variation with time of the reductive dissolution in 0·1*N*-hydrochloric acid of the oxide ignited at 1000° is shown in Fig. 7, and Fig. 8 gives the corresponding variation of the cathodic efficiency.

The effect of pH on the reductive dissolution in solutions of hydrochloric acid and the efficiency of reduction of the oxide ignited at 1000° are shown in Figs. 9 and 10; the range of pH covered in this examination was 0·0—2·0, the cell being too insensitive for higher values.

Effect of Different Acids.—The experiments determining the effect of pH on the reductive dissolution of the oxide ignited at 1000° were repeated, different solutions of sulphuric and perchloric acids being used. The results were the same, within the limits of experimental error, as those previously obtained with hydrochloric acid.

Two-stage Experiments.—It was now thought that reductive dissolution of ferric oxide powders was influenced by surface conductivity and consequently, according to Bevan, Shelton, and Anderson (*loc. cit.*), by the number of surface defects. It was shown by Pryor and Evans (*loc. cit.*) that certain acid pre-treatments, which were believed to alter the number of surface defects, greatly altered the rate of direct dissolution of α-ferric oxide powders. Two-stage experiments were, therefore, carried out to ascertain whether similar treatments had any effect on the rate of reductive dissolution.

FIG. 11.



In a typical experiment 1·0 g. of the oxide ignited at 1000° was exposed to 0·1*N*-hydrochloric acid for 20 hours, followed by filtration, careful washing, and drying in a desiccator. A 0·250-g. sample of the residue was subjected to direct attack by 0·1*N*-hydrochloric acid in the mercury cell for 1 hour and was found to lose 0·022%. A second sample subjected to reductive dissolution lost an additional 0·012% at a current efficiency of 6·5%. A sample of the oxide, which had not received any acid pre-treatment, would have suffered reductive dissolution to the extent of 0·023% at a cathodic efficiency of 10% under similar conditions.

In another typical experiment, 0·250 g. of oxide ignited at 1000° was subjected to cathodic treatment in 0·1*N*-hydrochloric acid for one hour. The current was then turned off, and direct dissolution allowed to proceed for a further hour. The quantity of oxide autoreduced in the first hour, calculated from previous experiments, was subtracted from the total iron content of the cathodic solution; the results showed that, in the second hour, only 0·005% of the oxide was dissolved by direct acid attack. A similar two-stage experiment, carried out without cathodic treatment, produced approximately 0·015% dissolution during the second hour's exposure to acid.

Reductive Dissolution under Anaerobic Conditions.—Experiments were carried out in de-aerated solutions with the mercury cell placed in a vacuum apparatus (Fig. 11). The cell was contained in a pressure desiccator, mounted on a movable trolley, so that it could be easily removed from the rest of the apparatus. Electrical connection was made to the cell through four stout brass rods forced through the rubber bung in the lid of the desiccator. All rubber joints in the apparatus were coated with picein wax to minimise access of air.

The electrolyte was partially freed from oxygen in the flask, *L*, by bubbling in nitrogen, previously purified by passing through reduced copper, nickel, and iron turnings at 450° for two hours; during this period the desiccator was thoroughly flushed out with nitrogen. The flask was then connected by a rubber tube to the tap *P*, in the desiccator lid, and the solution run into the mercury cell under reduced pressure. The desiccator was then evacuated with a "Hyvac" two-stage pump for ten minutes. During this operation the electrolyte boiled vigorously and expelled the gases dissolved in the solution. After ten minutes' pumping, purified nitrogen was readmitted, through tap *N*, and the desiccator flushed out for a further ten minutes. Taps *P* and *N* were then closed, and the desiccator isolated from the rest of the apparatus.

The oxide was introduced into the cell by a clockwork tipping device. The small tube, containing 0·25 g. of oxide, was supported in a horizontal position by a rubber band stretched between two pins. The tube could be released by movement of the minute finger of the clock, which was attached to the rubber band by a hook and a length of thread. Once released, the tube jettisoned its contents into the cell and the experiment could commence.

Results in the Absence of Oxygen.—The majority of the anærobic experiments were carried out on oxide ignited at 1000°—the type mainly used in previous experiments.

The variations, with time, of the percentage of reductive dissolution and the cathodic efficiency in 0·1N-hydrochloric acid are shown in Figs. 7 and 8. The rates of reductive dissolution are identical, within the limits of experimental error, with those previously obtained in solutions containing dissolved oxygen; the cathodic efficiency, however, is very much higher (Fig. 8) and in the first 15 minutes approaches 100%.

The relation between pH and both the percentage of reductive dissolution of the oxide ignited at 1000° and the cathodic efficiency, in different solutions of hydrochloric acid, is shown in Figs. 9 and 10. Again the rates of reductive dissolution are almost identical with those obtained in solutions of equivalent concentration containing dissolved oxygen, whilst the cathodic efficiencies are much higher.

An experiment on the oxide ignited at 385° showed that 0·14% was reductively dissolved, in one hour, in 0·1N-hydrochloric acid, at a current efficiency of 85%, as compared with 0·073% reductive dissolution at an efficiency of 25% in a solution of the same acid containing dissolved oxygen.

Discussion.

During the experiments previously described the electrode potential of the cathode never fell below −0·28 volt. Since Frumkin's results (*Discussions of Faraday Soc.*, 1947, **1**, 57) show that, at the experimental current density (approx. 10^{-4} amp./sq. cm.) the overpotential of hydrogen evolution in 0·1N-hydrochloric acid is approximately 0·95 volt, only a negligible fraction of the total cathodic current can be accounted for by this reaction.

It appears, therefore, that the two most important reactions taking place at the cathode are: (*a*) the reductive dissolution of ferric oxide; (*b*) the reduction of oxygen dissolved in the electrolyte.

In solutions containing dissolved oxygen it has been observed that the efficiency of the first process never exceeded 50% and seldom even 25%. Conditions present in this cell, however, favour the reduction of oxygen as this reaction takes place at the mercury surface. Reductive dissolution, on the other hand, involves the transference of electrons across the mercury–oxide interface and through the oxide itself. During the study of the reductive dissolution of ferric oxide films both alternative cathodic reactions occurred at the oxide–solution interface and so it is probable that, in this case, the efficiency of reductive dissolution was higher.

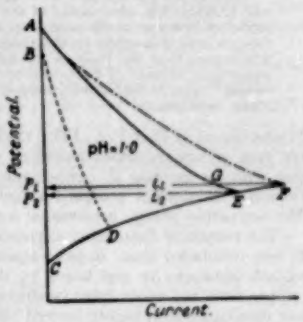
The rate of reductive dissolution and the percentage efficiency decrease as the temperature of ignition increases from 385° to 1000° (Figs. 5 and 6). The rate appears to be higher for oxide ignited at or below 300°, but the correction for the direct dissolution of these oxides is so high that the values are unreliable. According to the results obtained in Part I, conditions of pH should be favourable for rapid reductive dissolution, but in spite of this, both the efficiency and the rate of reduction are fairly low, and it may be that this is caused by low electronic conductivity of the oxide. Bevan, Shelton, and Anderson (*loc. cit.*) showed that the surface conductivity of massive α-ferric oxide was much higher than its bulk conductivity and depended largely on the number of defects present in the surface layers. Reductive dissolution must involve the conduction of electrons through the oxide, and so it is probable that surface conductivity is a most important factor. It was suggested by Pryor and Evans (*loc. cit.*) that the rate of direct attack on α-ferric oxide of acids which do not form soluble complexes with ferric ions depended on the number of defects in the surface; furthermore, increase of the temperature of ignition from 385° to 1000° resulted in a steady decrease in the rate of direct dissolution in 0·1N-hydrochloric acid owing to the fact that the oxides ignited at comparatively low temperatures contained a high number of defects "frozen-in" at the phase change at 300°; the powdered oxides ignited between 385° and 600°, which presumably contain this comparatively high number of defects, are fairly readily auto-reduced in the mercury cell (Fig. 5), and it can be seen, from Fig. 4, that the cathodic potentials during reductive dissolution of oxides ignited at 385° and 600° remain practically constant with time. Heating above the Tammann temperature—approximately 650° for α-ferric oxide—should result in a decrease in the number of defects, and it can be seen that the rate of reductive dissolution drops between ignition temperatures of 600° and 800°. It appears that the cathodic polarisation during autoreduction of the oxide ignited at 1000° increases continuously with time, probably owing to a progressive exhaustion of surface defects and consequently a reduction of the surface conductivity.

Practically all the reductive dissolution of the oxide ignited at 1000° occurs during the first 15 minutes' exposure to 0·1N-hydrochloric acid (Fig. 7). In direct dissolution also the rate is quickest during the first 15 minutes of the experiment, and so this additional close parallelism between direct and reductive dissolution supports the view that they both depend on the number of defects in the surface of the oxide; further confirmation was provided by two-stage experiments which showed that, once the surface defects originally present in the oxide surface had been largely removed by acid treatment, the rate of reductive dissolution decreased from 0·023% to 0·012%, in one hour, and the efficiency from 10% to 6·5%.

Direct dissolution in non-complex-forming acids was found to be independent of the acid radical, and a similar result was obtained during a study of reductive dissolution.

The rate of reductive dissolution and the efficiency increased with a decrease in pH value, as shown by Figs. 9 and 10. Since it was also found that higher currents flowed at lower pH values, this observation agrees with that of Campbell and Thomas (*Nature*, 1938, **142**, 253; *Trans. Electrochem. Soc.*, 1939, **76**, 303) who showed that, at high current densities, the importance of oxygen as a cathodic depolariser was smaller. Presumably at high current densities and rapid rates of reductive dissolution, the oxygen immediately surrounding the cathode is rapidly exhausted. Any subsequent reduction of oxygen will then be controlled by the rate at which it can diffuse to the cathode from the bulk of the solution. If the rate of reductive dissolution is high, this rate of diffusion will be slow by comparison and so the efficiency of reductive dissolution should be high.

FIG. 12.



CDEF = *Anodic polarisation curve.*
BD = *Oxygen reduction curve.*
AE = *Reductive dissolution curve.*
AF = *Total cathodic curve.*
(*Not to scale.*)

Reductive dissolution probably involves two stages, *i.e.*, reduction and direct dissolution of the product of reduction. The fact that cathodic reduction of oxide films, by means of a small constant current, can be achieved at higher pH values than autoreduction indicates that the overall reductive dissolution is not controlled by the direct dissolution of the product of reduction—at least at low pH values. The results of the two-stage experiments on the reductive dissolution of oxide powders are also in accord with this view.

In general, it can be seen that the removal of dissolved oxygen has practically no effect on the rate of reductive dissolution of ferric oxide ignited at 1000° but increases the cathodic efficiency of this process very considerably. These results are in accordance with high polarisation of the cathodic reaction and low polarisation of the anodic reaction. If the currents resulting from the two simultaneous cathodic reactions are summed graphically by Akimov's method (*Acta Physicochem. U.S.S.R.*, 1945, **20**, 809), it will be seen from Fig. 12 that in the presence of dissolved oxygen the total corrosion current is i_1 of which P_1G is devoted to reducing oxide and GF to reducing oxygen. If the oxygen is removed from solution the total corrosion current i_2 is all devoted to reducing oxide. The rate of reduction, which depends on the current flowing, is little different from that in the presence of oxygen (P_1G) provided that the slope of the anodic curve is low compared with that of the cathodic curve. The current efficiency, however, increases in this case from $100P_1G/P_1F$% to 100%. Thus it can be seen that the fact that oxygen removal only influences the efficiency of reduction of the oxide at 1000° is due to high polarisation of the cathodic reaction.

The rate of reductive dissolution of the oxide ignited at 385° appears to be increased by removal of oxygen. In this case, however, the polarisation of the cathodic reaction is smaller (Fig. 4), probably owing to the comparatively high number of defects. It would therefore be expected, in this case, that removal of oxygen would increase the rate of reductive dissolution of this oxide as well as the cathodic efficiency—as was found to be the case.

Conclusion.—A cell has been developed suitable for investigating the reductive dissolution of powdered samples of α-ferric oxide. A fixed mass of oxide is floated on mercury, and both the rate and the current efficiency of reductive dissolution are measured. It was shown that both the rate and the current efficiency of reductive dissolution decrease with an increase in the temperature of ignition of the oxide, with increasing duration of the experiment, and with an increase in pH of the electrolyte. The results obtained with solutions of sulphuric and

perchloric acid are identical, within the limits of experimental error, with those obtained in solutions of hydrochloric acid. When the solutions are de-aerated the current efficiency increases, but the rate of reductive dissolution is not significantly altered. This is believed to be due to the facts that reductive dissolution is highly polarised and that the influence of pH on the unpolarised potential of reductive dissolution is given by a term $(3RT/F) \log_e [H^+]$, while that on the alternative reduction of dissolved oxygen is given by $(RT/F) \log_e [H^+]$. The rôle of dissolved oxygen as a cathodic depolariser becomes more pronounced as the pH increases and the current density decreases.

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258. *The Reductive Dissolution of Ferric Oxide in Acid. Part III. The Mechanism of Reductive Dissolution.*

By M. J. Pryor.

This paper summarises the conclusions of the two previous papers on reductive dissolution and suggests the mechanism of the reaction. It is believed that the reductive dissolution of ferric oxide involves the combination of hydrogen atoms, discharged at the oxide surface, with oxygen ions, belonging to the oxide lattice, to form either hydroxyl ions or water molecules which pass into the bulk of the solution. This reaction liberates electrons which reduce an equivalent number of ferric ions to the ferrous condition, thus creating a series of the "metal-excess" type of defects in the oxide surface which will then become particularly susceptible to direct acid attack.

It was shown in Part I (*J.*, 1950, 1259) that, on dissolution of thin films of α-ferric oxide on iron, the rate of autoreduction increases with a decrease in film-thickness, with a decrease in pH and with an increase in temperature of the electrolyte. Potential measurements show that reductive dissolution is highly polarised and that the polarisation increases with a rise in pH. The activation energy determined from the temperature coefficient is about 8·5 kcals./g.-mol.

The reductive dissolution of powdered samples of α-ferric oxide was investigated in Part II. It was concluded that, at pH values below 2·0, reductive dissolution is controlled mainly by surface conductivity and hence by the number of surface defects. The removal of dissolved oxygen from the electrolytes produces no significant change in the rate of reductive dissolution, but results in much higher current efficiencies of reduction; the effect of dissolved oxygen as a cathodic depolariser becomes more pronounced as the current density decreases.

The reductive dissolution of ferric oxide was represented in Part I by the equation

$$Fe_2O_3 + 6H^+ + 2e = 2Fe^{++} + 3H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and it was considered that the reaction occurred in three simultaneous steps: (*a*) the conduction of electrons through the oxide; (*b*) the reduction of surface layers of the oxide to the ferrous condition; (*c*) the rapid direct dissolution of the product of reduction. In the majority of experiments the overall reaction is not controlled by the first step; in fact the only examples in which this step largely controls the overall reaction are during the reductive dissolution of silvery hiatus and thicker films and during the reductive dissolution of oxide powders, the conductivity of which is confined mainly to surface layers.

The results of the two-stage experiments described in Part II, and the fact that cathodic reduction of oxide films can take place at pH values as high as 5·0, indicate that, within the pH range of rapid autoreduction, the overall reaction is not controlled by stage (*c*).

Thus it appears that the step mainly controlling the rate of reductive dissolution of α-ferric oxide is step (*b*). Miley (*Carnegie Schol. Mem. Iron and Steel Inst.*, 1936, **25**, 197) pictured this step as the reduction of ferric oxide to ferrous oxide, but the author believes that the mechanism of the reduction is essentially similar to that suggested by Bevan, Shelton, and Anderson (*J.*, 1948, 1729) for the high-temperature reduction of semi-conducting oxides by gaseous hydrogen.

During autoreduction, electrons necessary for reductive dissolution are provided by the anodic dissolution of iron, and it was shown by Evans and Miley (*J.*, 1937, 1295) that one molecule of ferric oxide required two electrons for reduction. It is believed that the electrons discharge hydrogen ions at the oxide surface according to the equation

$$2H^+ + 2e = 2H \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Since the electrons have to pass through the oxide to the oxide–solution interface, it is this step that is influenced by the electronic conductivity of the oxide. The two hydrogen atoms, adsorbed on the oxide surface, then react with one oxygen ion, belonging to the oxide lattice, to give a water molecule which passes into the bulk of the solution :

$$\underset{\text{(adsorbed on the oxide)}}{2H} + \underset{\text{(belonging to the oxide lattice)}}{O''} = H_2O + 2e \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The two liberated electrons combine with the two neighbouring ferric ions and reduce them to the ferrous condition :

$$2Fe^{+++} + 2e = 2Fe^{++} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Thus two hydrogen atoms, discharged by two electrons produced at the anode, have created a defect of the " metal excess " type in the oxide surface. In the experiments of Bevan, Shelton, and Anderson (*loc. cit.*), the temperature was usually sufficiently high to allow these defects to diffuse into the interior of the oxide. Under the experimental conditions studied by the author, however, the temperature was never high enough to permit rapid self-diffusion and so it is believed that the defects created by this series of reactions remain in the surface layer.

The chemical composition of the product of reduction produced in reactions (3) and (4) is roughly that of ferrous oxide. The crystal structure will, however, be very different from that of the face-centred cubic ferrous oxide and will approximate to that of α-ferric oxide with one oxygen ion per molecule missing and the ferric ions replaced by ferrous ions.

It was suggested (Pryor and Evans, *J.*, 1949, 3330) that direct acid attack on α-ferric oxide took place mainly at isolated surface defects of this type, and that once the original surface defects were largely destroyed, the rate of attack rapidly decreased. During reductive dissolution, a large number of similar defects are continually produced in the oxide surface by the mechanism previously described; hence it would be expected that direct acid attack upon the reduced surface layers would be extremely rapid. The reactions believed to occur during reductive dissolution of one molecule of α-ferric oxide may be summarised by the sequence (2) and (3), followed by (4) and (5), the total result being (1).

$$(2Fe^{+++} + 2O'') + 2e = \underset{\text{(product of reduction)}}{(2Fe^{++} + 2O'')} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

$$\underset{\text{(product of reduction)}}{(2Fe^{++} + 2O'')} + 4H^+ = \underset{\text{(in solution)}}{2Fe^{++} + 2H_2O} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

This leads to an explanation of the remarkable difference in the rates of the direct and reductive dissolution of α-ferric oxide. The direct dissolution of the so-called α-ferric oxide is a slow process depending on lattice defects originally present in the oxide; their frequency depends on the previous history of the oxide, but in all cases they are few in number. The initial and comparatively rapid attack takes place at defects near to the surface, but, once these are destroyed, the rate of dissolution falls off as the more perfect parts of the oxide lattice are attacked. Since these defects not only involve the presence of ferrous ions but also loosen the lattice forces around neighbouring ferric ions, the iron in solution is partly in the ferrous and partly in the ferric condition. The reductive dissolution of α-ferric oxide is a much more rapid process since, here, a large number of defects are produced in the surface at a rate determined by the applied current. The entire surface of the oxide is continually converted into defects, with the result that the iron passing into solution is wholly in the ferrous condition.

It has been shown previously that the reductive dissolution of ferric oxide is mainly controlled by the production of defects in the surface as shown in equations (3) and (4); it is probable that this step, and in particular, the reaction between adsorbed hydrogen atoms and oxygen ions belonging to the oxide, *i.e.*, equation (3), is responsible for the high polarisation of the overall reaction. The comparatively high value of the activation energy of autoreduction, *i.e.*, 8·5 kcals./g.-mol., determined in Part I, probably refers mainly to this step in the overall reaction.

Several of the reactions that can take place at an iron cathode in solutions of low pH values are : (1) the reductive dissolution of the oxide film; (2) the reduction of dissolved oxygen; (3) the evolution of hydrogen. The first step in all these reactions is probably the discharge of hydrogen ions. These discharged ions may react with oxygen ions belonging to the ferric oxide lattice, in which case the oxide film will suffer reductive dissolution, they may reduce oxygen

dissolved in solution, or they may combine together to form molecules of hydrogen. Alternative cathodic reactions are, in fact, alternative reactions of hydrogen atoms discharged cathodically.

The mechanism suggested for the reductive dissolution of α-ferric oxide can be extended to include the cathodic reduction of cuprous and cupric oxides, and the sulphides of copper and silver. In these cases, however, the electrons liberated by the combination of adsorbed hydrogen atoms with oxygen (or sulphide) ions, belonging to the oxide (or sulphide) lattice, will probably reduce cuprous or silver ions directly to the metal, and cupric ions first to the cuprous condition and then to the metal.

The author expresses his thanks to Dr. U. R. Evans, in whose laboratory the work was carried out, for his encouragement and advice, and to the Department of Scientific and Industrial Research for financial assistance.

DEPARTMENT OF METALLURGY, UNIVERSITY OF CAMBRIDGE. [*Received, December 15th*, 1949.]

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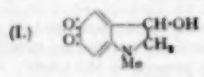
259. *The Chemistry of Adrenochrome and its Derivatives.*

By JOHN HARLEY-MASON.

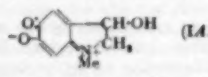
The reduction of adrenochrome (I) has been shown to give rise to two products: 5:6-dihydroxy-1-methylindole (II), and an intermediate zwitterion easily converted into 3:5:6-trihydroxy-1-methylindole (III). The latter product is also obtained by the action of alkali on (I), and on oxidation gives 5:6:5′:6′-tetrahydroxy-1:1′-dimethylindigo. From the reduction of 2-bromoadrenochrome, only 2-bromo-5:6-dihydroxy-1-methylindole could be isolated.

The oxidation of (II) and the conversion of (I) into "adrenaline black" have been studied, and the structure of the latter is discussed. The preparation of aqueous solutions of (I) by oxidation of adrenaline with buffered persulphate is described.

ADRENOCHROME (I) was first isolated by Green and Richter (*Biochem. J.*, 1937, **31**, 596), who obtained it by the oxidation of adrenaline with catechol oxidase in aqueous solution. The preparation was improved by Veer (*Rec. Trav. chim.*, 1942, **61**, 638), who employed silver oxide as oxidising agent, and subsequently by Buchnea (*C.I.O.S. Report* No. 259; a brief account of the method is given in the Experimental section, owing to the inaccessibility of the original). The structure (I) proposed by Green and Richter has been generally accepted, though it has been argued recently (Harley-Mason, *Experientia*, 1948, **4**, 307) that the zwitterionic *p*-quinonoid mesomeric structure (I*A*) makes a large contribution to the resonance hybrid.



(I.)

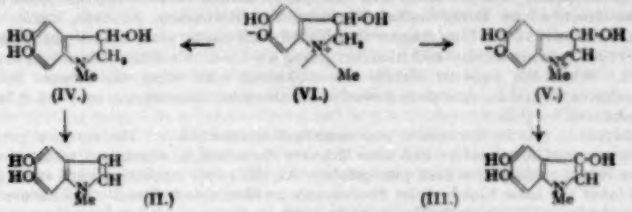


(I*A*.)

The pharmacological properties of (I) and its derivatives have excited considerable attention in recent years (cf. the review by Bacq, *J. Pharm. Exp. Therap.*, 1949, **95**, [ii], 1), and the present work is aimed at clearing up some of the discrepancies in the pharmacological literature by isolating pure materials from the rather complex transformation products of adrenaline, and submitting them to test independently.

The reduction of adrenochrome was first studied. On hydrogenation of an aqueous solution at room temperature and atmospheric pressure over palladium–charcoal, hydrogen uptake was found to cease when approximately *one* atom of hydrogen per mole of (I) had been absorbed. Ether-extraction of the resulting yellow solution afforded 5:6-*dihydroxy*-1-*methylindole* (II), which formed colourless needles, and gave a diacetate identical with that obtained by Bergel and Morrison (*J.*, 1943, 48). Evaporation of a portion of the aqueous solution gave no crystallisable product, but addition of alkali followed by acidification with acetic acid gave a yellow substance $C_9H_{11}O_4N$ which was formulated as 2:3:5:6-tetrahydroxy-2:3-dihydro-1-methylindole in a preliminary communication (Harley-Mason, *loc. cit.*). However, it was subsequently found that, on intensive drying, a molecule of water was lost, giving anhydrous 3:5:6-*trihydroxy*-1-*methylindole* (III); the original material was thus the corresponding *monohydrate* which retains the molecule of water rather firmly. The same results were obtained with sodium dithionite as the reducing agent, though satisfactory yields could only be obtained if the dithionite was fresh (and thus did not contain bisulphite formed by oxidation). Further, an excess of dithionite must be avoided, or the yield of (II) is much reduced, apparently owing to the formation of a bisulphite compound.

The mechanism of the reduction of (I) is thus of particular interest since, instead of the expected leuco-compound (IV), two products are obtained—one a dehydration product of (IV) and the other the zwitterion (V), isomeric with the original quinone. Moreover, these two products are found in approximately equal quantities. This suggests strongly that they are formed by the disproportionation of a common intermediate, the semi-quinone (VI) formed by addition of a hydrogen atom to (I) as represented in the scheme. The ready dehydration of

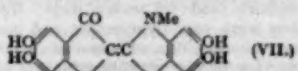


(IV) to (II) is substantiated by the work of Wiesner (*Biochem. J.*, 1942, **313**, 48) who examined the polarographic reduction of adrenochrome and found that the initial reduction product [which could be re-oxidised to (I)] was rapidly and irreversibly transformed into a product which could not be re-oxidised to (I).

Green and Richter (*loc. cit.*) observed that the reduction of adrenochrome gave an optically active solution; this result has been confirmed and moreover the rotation does not change during 24 hours at room temperature. This indicates clearly that the optical activity cannot be due to (IV) and supports the structure (V) assigned to the zwitterionic reduction product which was not isolated. On treatment with alkali, (V) undergoes irreversible prototropic change to give (III) which is of course optically inactive. The course of this change in very dilute solution was followed by examining the change in the absorption spectrum. It should be noted that Wiesner's polarographic studies (*loc. cit.*) failed to disclose any evidence of semiquinone formation; it is possible that under these conditions direct reduction to (IV) occurs. The only alternative explanation of the previous results, namely that reduction and isomerisation occur simultaneously, seems very unlikely, for it is improbable that these two processes occur at equal rates even when two different reducing agents are employed.

The trihydroxy-compound (III) is bright yellow and is sparingly soluble in water and in organic solvents, giving yellow solutions with a very powerful green fluorescence; dilute solutions soon absorb oxygen from the air, and the fluorescence disappears. Treatment of (III) with acetic anhydride and pyridine gives **3 : 5 : 6-*triacetoxy*-1-*methylindole*** which is colourless and non-fluorescent, and can also be obtained by the action of the same reagents on adrenochrome itself, rearrangement as well as acetylation occurring in the latter case. Alkaline hydrolysis of the triacetate in the absence of air gives (III). (III) may also be obtained—and this is the more convenient method of preparation—by the direct action of alkali on an aqueous solution of adrenochrome, followed by acidification with acetic acid [cf. Fischer, *Bull. Soc. chim. Belg.*, 1949, **58**, 205, who clearly obtained the monohydrate of (III)]. It is very probable that (III) is the compound responsible for the green fluorescence observed in determination of adrenaline by Gaddum and Schild's method (*J. Physiol.*, 1934, **80**, 9P) in which the adrenaline is oxidised in alkaline solution: the adrenochrome first produced would be isomerised to (III) by the alkali. A similar suggestion has been put forward by Ehrlen (*Farm. Revy.*, 1948, **47**, 242). Since our work was completed, the isolation of (III) has been reported by Lund (*Acta Pharmacol.*, 1949, **5**, 121), who also records the firm retention of water by the monohydrate.

Acid solutions of (III) absorb oxygen from the air slowly in the cold but more rapidly at the boiling point, giving **5 : 6 : 5′ : 6′-*tetrahydroxy*-1 : 1′-*dimethylindigo*** (VII) as a greenish-black precipitate, characterised as its ***tetra-acetate.*** (VII) closely resembles the unmethylated



compound synthesised previously (Harley-Mason, *J.*, 1948, 1244) in retaining a molecule of water which could not be removed by intensive drying and in giving an intensely permanganate-

coloured solution in aqueous alkali. Its solution in pyridine was however green, in contrast with the blue solution given by the unmethylated compound; this bathochromic effect of *N*-methylation is observed with indigo itself.

The dihydroxyindole (II) is colourless and readily soluble in water and organic solvents, giving, in the latter, solutions which show a rather weak bluish-violet fluorescence in ultra-violet light. Alkaline solutions absorb oxygen from the air very rapidly, giving at first a deep blue colour which rapidly becomes violet and then brown (cf. the oxidation of the unmethylated compound as described by Beer, Clarke, Khorana, and Robertson, *J.*, 1948, 2223). When the solution while still at the blue stage was acidified with acetic acid, a dark precipitate was obtained, partly soluble in alcohol and in ether, giving a deep-blue solution which was stable for several days. When the aqueous filtrate was extracted with ether, the almost colourless ethereal solution exhibited an extremely powerful bluish-violet fluorescence, very much stronger than that exhibited by (II).

The oxidation of (II) by tyrosinase was examined qualitatively. The reaction proceeded fairly rapidly at room temperature and after 2 hours the solution, which had assumed a dirty violet colour, began to deposit a dark precipitate. At this point extraction with ether gave in the ethereal layer the same bluish-violet fluorescence as that noted above. The nature of this fluorescent material, which is probably an early stage in the oxidative polymerisation of (II), is at present under investigation. After oxidation for 24 hours, a copious black precipitate was obtained and an ethereal extract was no longer fluorescent. It is particularly significant that at no period during the oxidation was there any indication of the formation of the indoxyl (III) which, if formed, should have been easily detectable by its intense green fluorescence. This suggests that melanin formation does not involve oxidation at position 3, at any rate as an initial stage.

It has long been known that solutions of adrenaline on oxidation give at first a red colour and then a brown or black precipitate of "adrenaline black" (VIII). Clearly the formation of adrenaline black proceeds *via* adrenochrome, and it has now been found that the transformation from adrenochrome does not require further consumption of oxygen. After storage for 24 hours under nitrogen at room temperature, an aqueous solution of (I) had decomposed completely, giving a precipitate of (VIII) in 75% yield. The yellowish-brown aqueous filtrate on extraction with ether yielded a trace of (II). Addition of alkali to the aqueous filtrate produced a green fluorescence indicating the formation of (III), though the amount formed was too small for isolation. Evidently then, some isomerisation of (I) also occurs. When dried at room temperature, (VIII) gave analytical figures corresponding fairly well to an empirical formula $C_9H_9O_4N$. It forms a black powder, insoluble in most organic solvents with the exception of pyridine, but soluble in aqueous alkalis to give a dark greenish-brown solution. Sodium dithionite reduces an aqueous suspension to an insoluble yellowish-brown leuco-compound, which is readily re-oxidised.

The dihydroxy-compound (II) is a reduction product of (I) and, since the formation of adrenaline black takes place in the absence of oxygen, the process must clearly involve to some extent an oxido-reduction. It will be noted that the empirical formula of (VIII) contains one atom of oxygen more than the original adrenochrome. Moreover the 75% yield of (VIII) obtained indicates clearly that the process cannot involve the simple reaction:

$$\underset{\text{(I.)}}{2C_9H_9O_3N} \longrightarrow \underset{\text{(II.)}}{C_9H_9O_3N} + \underset{\text{(VIII.)}}{C_9H_9O_4N}$$

which would necessitate a maximum yield of 50%; this process is in any case hardly possible since (II) is in fact not a *direct* reduction product of (I), but rather a dehydration product of the unstable leuco-compound (IV).

The most likely explanation is that (VIII) contains tightly bound water [compare (VII), the unmethylated analogue of (VII), and (III)] and that its composition approximates in fact to $C_9H_7O_3N,H_2O$ or perhaps $C_9H_5O_3N,2H_2O$.

Some indication that this may be the case was obtained on micro-analysis of specimens of (VIII) dried at 100° over phosphoric oxide for several days; these specimens certainly had a lower oxygen content, but they were very hygroscopic and consistent results could not be obtained. It would seem that the retention of water occurs in no precise stoicheiometric ratio; this is not surprising in view of the amorphous nature of (VIII) and the fact that it appears to be polymeric.

The anærobic conversion of adrenochrome into adrenaline black was strongly catalysed by mineral acid. In 5% aqueous solution, acidified to *ca.* pH 2 with hydrochloric acid, (I)

decomposed completely to (VIII) in 15 minutes at room temperature, whereas, in the absence of acid, decomposition required 24 hours.

Cohen (*Bull. Soc. chim. Biol.*, 1946, **28**, 104, 107, 354) has suggested that the formation of (VIII) from (I) proceeds *via* the *o*-quinonoid oxidation product of (III), 3-hydroxy-1-methylindole-5 : 6-quinone (described as "oxo-adrenochrome"), which then undergoes chain polymerisation by intermolecular condensation at the 2- and 5-positions with elimination of water. Various attempts were made to oxidise (III) to "oxo-adrenochrome" but with no indication of success, and the only recognisable oxidation product obtained in all cases was the tetrahydroxyindigo (VII), which was formed with great ease and of course differs completely from (VIII). Cohen's structure for (VIII) is thus very improbable, and in any case it should be noted that a mechanism involving condensation of an indoxyl in the 2-position with the carbonyl group of a quinone is *a priori* improbable since both indoxyl and (III) are simply oxidised to the corresponding indigos by *p*-benzoquinone and do not condense with it. The same objections apply to the structure for dopa-melanin proposed by the same author. Furthermore, the melanin structure proposed by Burton (*Chem. and Ind.*, 1948, 313) contains repeating hydroxyindoxyl units and by analogy with (III) it would be expected that further oxidation to indigoid products would occur extremely readily.

2-Bromoadrenochrome was prepared by a slight modification of the method described by Green and Richter (*loc. cit.*); its formation from (−)-adrenaline generates a new asymmetric centre so that two diastereoisomeric products should be obtained. It is possible that bromoadrenochrome as obtained is such a mixture, but owing to difficulty of recrystallisation separation was not attempted. Reduction of a warm aqueous suspension of the bromo-compound with sodium dithionite gave a considerable amount of insoluble tar; after filtration the yellow filtrate deposited, on cooling, *2-bromo-5 : 6-dihydroxy-1-methylindole* as almost colourless needles, characterised by a *diacetate*. No crystalline product could be isolated from the tar.

For the preparation of aqueous solutions of adrenochrome an alternative was sought to the use of silver oxide as oxidising agent. Sodium persulphate can be used advantageously, but the presence of a buffer such as sodium acetate or sodium hydrogen carbonate is necessary. The addition of a trace of a ferrous salt accelerates the reaction considerably. Solutions of adrenochrome prepared in this way can be used conveniently to prepare derivatives such as the oxime and semicarbazone ("Adrenoxyl"), but the yields of (II) and (III) obtained from such solutions are lower than those obtained when silver oxide is employed.

Certain observations in the literature concerning adrenochrome are explicable in the light of the present work. Bergel and Morrison (*loc. cit.*) examined the oxidation of adrenaline by oxygen in the presence of a palladium–charcoal catalyst. The deep-red solution obtained was reduced and acetylation then gave a small amount of material, m. p. 105—110°. This was clearly a mixture of the diacetate, m. p. 104—105°, of (II) and the triacetate, m. p. 112—113°, of (III). Beauvillain and Sarradin (*Bull. Soc. chim. Biol.*, 1948, **30**, 478), on decomposition and reduction of aqueous solutions of (I), observed the presence of two substances, one soluble in ether and exhibiting a blue fluorescence and the other soluble in water exhibiting a greenish-yellow fluorescence; these are evidently (II) and (III) respectively.

A pharmacological investigation of (III) is now being undertaken.

Experimental.

Adrenochrome (I).—(*a*) (After Buchnea, *loc. cit.*) (−)-Adrenaline (18·3 g., 0·1 mol.) was dissolved in dry methanol (500 ml.) containing formic acid (10 ml.). Freshly precipitated silver oxide (73 g., 0·31 mol.) was added and the mixture shaken vigorously for 3 minutes. The temperature rose to 40°. Silver and excess of silver oxide were removed by filtration, and the residue was washed with methanol (100 ml.) at 40°. The deep-red filtrate and washings were cooled to −20° in a carbon dioxide freezing mixture, and after ½ hour the precipitated deep-red crystals were filtered off, washed with a little cold methanol followed by dry ether, and transferred immediately to a vacuum-desiccator which was kept in the dark. The yield was 7·8 g. of anhydrous material (Found: C, 60·7; H, 5·4; N, 7·8. Calc. for $C_9H_9O_3N$: C, 60·3; H, 5·0; N, 7·8%).

(*b*) (−)-Adrenaline (2 g.) was suspended in water (70 ml.), and dilute hydrochloric acid was added dropwise, with shaking, until a clear solution was obtained. Silver oxide (8 g.) was added, the mixture shaken vigorously for 5 minutes and then filtered. The aqueous solution of adrenochrome thus obtained was stable for about 12 hours at 0°.

(*c*) (−)-Adrenaline (1·8 g.) was suspended in water (70 ml.), and acetic acid was added dropwise until a clear solution was obtained. Sodium acetate (3 g.) and sodium persulphate (5 g.) were then added, followed by one drop of 1% ferrous sulphate solution. The mixture was kept at room temperature (20°) for 1·5 hours with frequent shaking, and the clear deep-red solution of adrenochrome thus obtained was used at once.

Reduction of Adrenochrome by Hydrogenation.—Adrenochrome (1 g.) in water (20 ml.) was hydrogenated over a palladium–charcoal catalyst at room temperature and atmospheric pressure. 64 Ml.

(N.T.P.) of hydrogen were absorbed in 20 minutes. A repetition of the experiment gave an uptake of 65·5 ml. [Calc. for 1 atom of hydrogen per mole. of (I), 62·5 ml.]. The yellow solution thus obtained was extracted with peroxide-free ether (3 × 15 ml.), the extract dried (Na_2SO_4), and the ether removed, leaving a yellow gum. Two recrystallisations from light petroleum (b. p. 100—120°) gave colourless needles of 5 : 6-*dihydroxy*-1-*methylindole* (II) (0·3 g.), m. p. 136° (decomp.) (Found : C, 66·2; H, 5·5; N, 8·6. $C_9H_9O_2N$ requires C, 66·3; H, 5·5; N, 8·7%). (II) is very soluble in ether, alcohol, or ethyl acetate, moderately soluble in water or benzene, and sparingly soluble in light petroleum. The crystals darken slowly on exposure to air. A deep red colour is given with the Ehrlich reagent. When a drop of dilute sodium hydroxide was added to an aqueous solution, very rapid oxidation occurred, giving initially a deep purple colour, becoming dirty violet after a few seconds, then brown, and eventually a brownish-black precipitate was deposited. When the solution, while still at the purple stage, was acidified with acetic acid, a dark precipitate was obtained. This was filtered off and the filtrate was extracted with ether. The colourless ethereal extract displayed a very powerful bluish-violet fluorescence. The precipitate was partly soluble in alcohol or ether, giving a deep-blue solution.

Acetylation of (II) (0·2 g.) with acetic anhydride (5 ml.) and pyridine (5 ml.) for 24 hours at room temperature, followed by pouring the mixture into water, and recrystallisation of the precipitate from benzene–light petroleum (b. p. 80—100°), gave 5 : 6-diacetoxy-1-methylindole, colourless prisms, m. p. 104—105° (Found : C, 62·9; H, 5·4. Calc. for $C_{13}H_{13}O_4N$: C, 63·2; H, 5·3%). Bergel and Morrison (*loc. cit.*) give m. p. 100—101°.

The yellow aqueous solution after extraction of (II) was made alkaline with 2*N*-sodium hydroxide, a deep-yellow solution with a powerful green fluorescence being obtained. This was acidified with acetic acid, and on storage at 0° small yellow prisms of 3 : 5 : 6-*trihydroxymethylindole monohydrate* (0·32 g.), m. p. 228—232°, slowly separated. After recrystallisation from water containing a little sodium dithionite to prevent oxidation, the compound had m. p. 230—232° (Found : C, 55·0; H, 5·8; N, 7·1. $C_9H_9O_3N,H_2O$ requires C, 54·9; H, 5·6; N, 7·1%). When dried at 100° in a high vacuum over phosphoric oxide for 3 days the crystals fell to a yellow powder, which is the anhydrous *indole*, decomposing, without melting, at 285° (Found : C, 60·0; H, 5·3; N, 7·7. $C_9H_9O_3N$ requires C, 60·3; H, 5·0; N, 7·75%). The trihydroxy-compound is readily soluble in sodium hydroxide, sparingly soluble in water, alcohol, acetic acid, or ethyl acetate, and almost insoluble in ether or benzene. The yellow solutions are oxidised in air, becoming brown, and the fluorescence disappears. With Ehrlich's reagent, a deep violet colour is given in the cold.

Acetylation of the trihydroxy-compound (0·2 g.) with acetic anhydride (5 ml.) and pyridine (5 ml.) for 36 hours at room temperature, followed by pouring the mixture into water and recrystallisation of the precipitate from benzene, gave 3 : 5 : 6-*triacetoxy*-1-*methylindole*, colourless prisms, m. p. 112—113° (Found : C, 58·4; H, 5·2. $C_{15}H_{15}O_6N$ requires C, 58·5; H, 5·5%).

The triacetate was also obtained directly from adrenochrome. Adrenochrome (1 g.) was dissolved in pyridine (10 ml.), and acetic anhydride (10 ml.) added. The mixture was kept for 36 hours at room temperature, the colour changing from red to pale brown, and was then poured into water. After 2 hours at 0°, the precipitate was collected and twice recrystallised from benzene. The yield was 0·6 g.

The triacetate (0·5 g.) was hydrolysed by refluxing for 1 hour with 2*N*-sodium hydroxide (20 ml.) containing a little sodium dithionite, under nitrogen. The deep-yellow solution was cooled and acidified with acetic acid and on storage at 0° deposited the monohydrate of (III) as small yellow prisms.

Preparation of (III) *directly from Adrenochrome.*—Adrenochrome (1 g.) was dissolved in water (30 ml.), and 2*N*-sodium hydroxide (8 ml.) added with stirring. The colour changed from red to deep yellow, and a powerful green fluorescence appeared. A little sodium dithionite was added to prevent oxidation, and the solution acidified with acetic acid. The trihydroxy-compound rapidly separated and after 2 hours at 0° was collected and recrystallised from water containing sodium dithionite. The yield was 0·65 g. of monohydrate. The same result was obtained with a solution of (I), prepared as described in (*b*) and (*c*) above; in the latter case the yield was smaller.

Reduction of Adrenochrome by Sodium Dithionite.—To a solution of adrenochrome (1 g.) in water (30 ml.) solid sodium dithionite was added with stirring until the initial deep red colour became yellow. The resulting solution was worked up as described above for the hydrogenation, giving (II) (0·32 g.) and (III) (0·28 g.). With solutions of (I) prepared as in (*b*) and (*c*) above similar results were obtained; in the latter case the yield of (II) was very poor. An experiment in which an old sample of dithionite, (containing sodium hydrogen sulphite) was employed gave almost negligible yields, and other experiments in which an excess of dithionite was added gave poor yields of (II).

A solution of adrenochrome (0·1 g.) in water (10 ml.) was reduced with dithionite and examined polarimetrically; at 18° a rotation of −0·53° was observed (10-cm. tube). If half of the adrenochrome is converted into the zwitterion (V) this corresponds to a value $[\alpha]_D^{18}$ −106° for this compound. The rotation was unchanged after 24 hours.

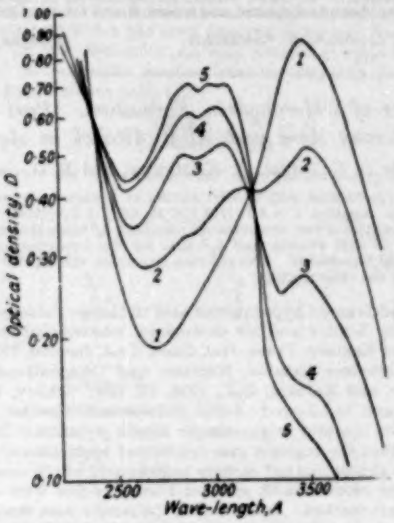
The conversion of the zwitterion (V) into the trihydroxyindole (III) with alkaline catalysis was followed spectrophotometrically. A solution of (I) (1·5 g.) in water (30 ml.) was reduced with dithionite and (II) extracted with ether as above; it was then diluted 5000-fold and the absorption determined (curve 1); $\lambda_{max.}$ = 3470; $\varepsilon_{max.}$ = 7700. To another sample of the solution a drop of 2*N*-sodium hydroxide was added and after 5 seconds a drop of acetic acid. The absorption was then determined (curve 2). Curves 3, 4, and 5 were determined exactly similarly after time intervals of 1, 5, and 20 minutes respectively. The last represents complete conversion into (III); $\lambda_{max.}$ = 2860 and 3050; $\varepsilon_{max.}$ = 6700.

5 : 6 : 5′ : 6′-*Tetrahydroxy*-1 : 1′-*dimethylindigo* (VII).—(*a*) 3 : 5 : 6-Trihydroxy-1-methylindole (0·5 g.) was dissolved in *N*-sodium hydroxide (5 ml.), and the solution diluted to 100 ml. and then acidified with hydrochloric acid. After the mixture had been kept for 10 days at room temperature exposed to the air with frequent shaking, the black precipitate which had slowly accumulated was collected. It was purified by dissolution in dilute sodium hydroxide under nitrogen, the solution was filtered, and the product was re-precipitated by acetic acid. The *indigo* was collected and dried at 100° in a high vacuum over phosphoric oxide (Found : C, 57·8; H, 4·5; N, 7·4. $C_{18}H_{14}O_4N_2,H_2O$ requires C, 58·1; H, 4·3;

N, 7·8%). It formed a greenish-black powder, soluble in pyridine, and sparingly soluble in acetic acid, giving deep green solutions. It was also soluble in sodium hydroxide, giving an intense permanganate-coloured solution, which rapidly oxidised on exposure to air, becoming brown. Reduction with dithionite gave a yellow vat.

(*b*) **3 : 5 : 6-Trihydroxy-1-methylindole** (0·2 g.) was dissolved in acetic acid (50 ml.), and the solution heated on a boiling water-bath for 2 hours with free access to air and frequent shaking. After cooling, the black precipitate was collected and purified as above.

Tetra-acetate of (VI).—(VII) (0·1 g.) was dissolved in pyridine (5 ml.), and acetic anhydride (5 ml.) added. After 3 days at room temperature the mixture was poured into water, and the green precipitate collected. The material proved too insoluble for recrystallisation and was purified by solution in pyridine, filtration, and precipitation by the addition of ethyl acetate. **5 : 6 : 5′ : 6′-*Tetra-acetoxy*-1 : 1′-*dimethylindigo*** formed a deep green powder, almost insoluble in all solvents with the exception of pyridine (Found : C, 58·8; H, 5·3; N, 5·2. $C_{34}H_{34}O_{12}N_2$ requires C, 59·3; H, 4·9; N, 5·3%).



Light absorption, at pH 4—4·5, in water of :

(1) *the zwitterion* (V);
(2) *mixture of* (V) *and* (III) *after* 5 *seconds' isomerisation ;*
(3) ,, ,, ,, 1 *minute's* ,,
(4) ,, ,, ,, 5 *minutes'* ,,
(5) **3 : 5 : 6-*Trihydroxy*-1-*methylindole*** (III) [20 *minutes' isomerisation of* (V)].

Formation of Adrenaline Black (VIII) *from* (I).—Adrenochrome (2 g.) was dissolved in air-free distilled water (30 ml.), and the solution transferred to a tightly-stoppered flask under nitrogen. After 48 hours at room temperature the deep red colour had become yellowish-brown and a copious precipitate of (VIII) had formed. The precipitate was collected, well washed with air-free water, and dried over phosphoric oxide (yield 1·5 g.) (Found : C, 54·7; H, 4·9; N, 7·0. $C_9H_9O_4N$ requires C, 55·4; H, 4·6; N, 7·2%). Prepared in this way, adrenaline black was a jet-black amorphous powder, almost insoluble in all organic solvents except pyridine in which it gave a greenish-brown solution. It was also soluble in sodium hydroxide, giving a similar coloured solution and was re-precipitated by the addition of acid. An aqueous suspension was slowly reduced by sodium dithionite, giving an insoluble yellowish-brown leuco-compound which was readily re-oxidised on exposure to air.

The aqueous filtrate from the solution of (VIII) was extracted with ether; removal of the ether yielded a very small amount of (II). The aqueous portion was made alkaline and then acidified with acetic acid; the characteristic green fluorescence of (III) was observed, but the amount was too small for isolation.

2-Bromoadrenochrome.—(−)-Adrenaline (1·8 g.) was suspended in water (100 ml.) in a stoppered bottle, and acetic acid added until all was dissolved. Sodium acetate (4 g.) was added, followed by bromine (1·5 ml.) which was added dropwise from a burette, with vigorous shaking between each addition. The product separated as deep-red prisms during the addition, which required 15—20 minutes. The mixture was kept at 0° for 1 hour, and the product then filtered off and washed with

ice-cold water. It was at once transferred to a vacuum desiccator, and was stable for about a week at room temperature. The yield was 1·3 g.

2-Bromo-5 : 6-dihydroxy-1-methylindole.—The above compound (0·5 g.) was suspended in water (20 ml.) at 40°, and sodium dithionite was added with very vigorous shaking. After a few minutes the solution became bright yellow and a dark tar separated. The tar was removed by filtration and the filtrate on cooling deposited yellow needles of impure material. After recrystallisation from benzene–light petroleum (b. p. 80—100°), colourless needles of *2-bromo-5 : 6-dihydroxy-1-methylindole*, m. p. 121—123° (decomp. : softening at 118°) were obtained (Found : C, 44·9; H, 3·5; Br, 32·8. $C_9H_8O_2NBr$ requires C, 44·6; H, 3·3; Br, 33·0%). The material rapidly darkened on storage.

This product (0·2 g.) was dissolved in pyridine (3 ml.), acetic anhydride (3 ml.) added, and the mixture kept for 24 hours at room temperature and then poured into water. The precipitate was collected and recrystallised from methanol (charcoal), giving colourless prisms of *2-bromo-5 : 6-diacetoxy-1-methylindole*, m. p. 164° (Found : C, 47·7; H, 3·8. $C_{13}H_{12}O_4NBr$ requires C, 47·85; H, 3·7%).

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260. *The Kinetics of Chlorohydrin Formation. Part I. The Reaction between Hypochlorous Acid and Allyl Alcohol in Aqueous Solution.*

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The addition of hypochlorous acid to allyl alcohol in aqueous solution has been found to conform to the kinetic equation $v = k_2^{\mathrm{I}}[\mathrm{HOCl}][\mathrm{C_3H_5{\cdot}OH}] + k_2^{\mathrm{II}}[\mathrm{HOCl}]^2$, where k_2^{I} and k_2^{II} are the specific reaction rates of two simultaneous reactions, k_2^{I} being that for the direct addition of hypochlorous acid to allyl alcohol, and k_2^{II} that for the formation of chlorine monoxide from hypochlorous acid in solution. The chlorine monoxide reacts with allyl alcohol as fast as it is formed to give the chlorohydrin.

KINETIC studies on the addition of hypochlorous acid to olefinic substances in aqueous solution have been carried out by Schilov and his co-workers, who studied the rates of addition to crotonic acid (Schilov and Kaniaev, *Trans. Inst. Chem. Tech. Ivanovo*, 1935, 19; *J. Phys. Chem. Russia*, 1934, **5**, 654), ethylene (Schilov, Kaniaev, and Otmennikova, *ibid.*, 1936, **8**, 909; Schilov, Soloduschenkov, and Kurakin, *ibid.*, 1939, **13**, 759; Schilov, Kaniaev, Domina, and Ionina, *ibid.*, p. 1242), and but-2-ene-1 : 4-diol (Schilov and Kaniaev, *ibid.*, 1937, **10**, 123). In no case did the results conform to any simple kinetic equation. In the case of ethylene, Schilov *et al.* observed that the reaction rate conformed approximately to the equation $v = k_2[\mathrm{HOCl}]^2$, where k_2 was almost but not entirely independent of the concentration of ethylene. The results of studies on crotonic acid and but-2-ene-1 : 4-diol were more complex and no satisfactory conclusion was reached. In each case, the results were rendered more complicated since these investigators studied the effects of addition of hydrochloric acid, which would react with the hypochlorous acid to give molecular chlorine. The rate of addition of chlorine to the double bond is some 100,000 times greater than that of hypochlorous acid (Schilov, Kaniaev, and Otmennikova, *loc. cit.*).

The major product with allyl alcohol is the chlorohydrin, 2-chloropropane-1 : 3-diol (Smith, *Z. physikal. Chem.*, 1918, **92**, 717). Earlier work by Henry (*J. pr. Chem.*, 1874, **10**, 185) reports the product as 3-chloropropane-1 : 2-diol. By analogy with bromine addition in aqueous media, where, following the addition of cationic bromine, the reaction is completed by any suitable anion (Francis, *J. Amer. Chem. Soc.*, 1925, **47**, 2344; Robinson, "Outline of an Electrochemical Theory of the Course of Organic Reactions," Institute of Chemistry, 1932, p. 16), hypochlorous acid presumably donates its chlorine atom to the more negative unsaturated carbon atom, the reaction being completed by acceptance by the other carbon atom of a hydroxyl ion, present as such in the aqueous solution or relinquished by a water molecule. This should lead to the formation of the 2-chloro-derivative. Whether the orientation of the addition is affected by the presence of peroxides (cf. Kharasch and Mayo, *J. Amer. Chem. Soc.*, 1933, **55**, 248) is uncertain, but redistillation of the allyl alcohol gave no appreciable alteration in its reactivity.

In a preliminary experiment, the velocity of reaction between hypochlorous acid and allyl alcohol in equal concentrations (0·002M.) was carried out, and the results were found to conform to the second-order velocity equation, 1/titre being a linear function of time; the values of k_2 are given in Table I, time being in minutes. When this same reaction was carried out in the presence of a borate buffer of pH 10, in which the hypochlorous acid is 99·8% ionised, very

little reaction occurred in the same period of time (Table I) indicating that the reaction involves un-ionised hypochlorous acid and not the hypochlorite ion.

TABLE I.

$[HOCl]_0 = [C_3H_5{\cdot}OH]_0 = 0{\cdot}002$ mole $l.^{-1}$. Titres in ml. of $x/500$-$Na_2S_2O_3$. Temp.: $25{\cdot}00° \pm 0{\cdot}01°$.

Time		0	2	3	5	7	9	11	13	15	17
Titre	(*a*)	18·3	—	17·1	16·6	16·0	15·45	15·0	14·5	14·0	13·5
k_1		—	—	11·7	10·2	10·3	10·2	10·0	10·1	10·2	10·5
Titre	(*b*)	18·8	18·5	—	—	—	—	—	—	—	18·7

(*a*) Unbuffered. (*b*) Buffered to pH 10.

The results of experiments showing the effect at $25{\cdot}00° \pm 0{\cdot}01°$ of varying the concentration of allyl alcohol and hypochlorous acid are shown in Tables II—V, where: a = initial concn. of hypochlorous acid in moles $l.^{-1}$; b = initial concn. of allyl alcohol in moles $l.^{-1}$; x = amount in moles $l.^{-1}$ of either reactant which has been removed in time t; t = time in minutes; k_1 = specific reaction rate for the *first*-order reaction involving hypochlorous acid, *i.e.*, $k_1 = (2{\cdot}303/t)\log_{10} a(a-x)$; k_2' = specific reaction rate for the *second*-order reaction involving both allyl alcohol and hypochlorous acid, *i.e.*,

$$k_2' = \frac{2{\cdot}303}{(b-a)t}\log_{10}\frac{a(b-x)}{b(a-x)};$$

k_2'' = specific reaction rate for the *second*-order reaction involving hypochlorous acid alone, *i.e.*, $k_2'' = x/[at(a-x)]$.

TABLE II.

$a = 0{\cdot}002$ mole $l.^{-1}$.

10^3b.	k_2'.	k_2''.
2	—	9·8
4	5·3	11·0
6	4·6	13·1
8	3·9	—

TABLE III.

Values of k_1 in $min.^{-1}$ ($\times 10^3$).

a	2	2	4	4
b	2	4	2	4
k_1	1·63	1·97	3·00	3·53

TABLE IV.

$a = 0{\cdot}002$ mole $l.^{-1}$.

10^3b.	10^3k_1.	k_1/b.	10^3b.	10^3k_1.	k_1/b.	10^3b.	10^3k_1.	k_1/b.
2	1·69	8·45	8	2·66	3·33	40	8·74	2·19
4	1·98	4·95	10	3·21	3·21	60	12·41	2·07
6	2·33	3·88	20	5·17	2·59	80	16·80	2·10

TABLE V.

$b = 0{\cdot}05$ mole $l.^{-1}$

10^3a (mole $l.^{-1}$).	10^3k_1 ($min.^{-1}$).
2	10·0
3	11·3
4	11·9

The results expressed in Tables II and III, which correspond to relatively low concentrations of allyl alcohol, show that the reaction is predominantly of the second order with respect to hypochlorous acid. In Table III, it is seen that the effect of doubling the concentration of the acid is nearly to double the value of k_1. Thus at low concentrations of the alcohol, $v \approx k_2''[HOCl]^2$. However, k_2'' is clearly not independent of the alcohol concentration.

The results expressed in Table IV show that k_1 becomes increasingly dependent on the alcohol concentration as the latter increases, and approaches proportionality with such concentration at $[C_3H_5{\cdot}OH] \approx 0{\cdot}06$ mole $l.^{-1}$. Thus at high concentrations of the alcohol, the reaction is predominantly of first order with respect to hypochlorous acid. The results given in Table V confirm this conclusion. At low concentrations (0·002M.) of the alcohol, doubling the concentration of hypochlorous acid quadruples the rate, whereas at high concentrations (0·05M.) the rate conforms to the expression $v = k_2'[HOCl][C_3H_5{\cdot}OH]$.

This change in the nature of the reaction is of the same type as that observed in similar addition reactions by Schilov *et al.* (*loc. cit.*) but for which no explanation was advanced. The present authors suggest that the results may be simply explained by assuming a kinetic equation of the form

$$v = k_2^{\mathrm{I}}[HOCl][C_3H_5{\cdot}OH] + k_2^{\mathrm{II}}[HOCl]^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where at high concentrations of the alcohol, the term $k_2^{\mathrm{I}}[HOCl][C_3H_5{\cdot}OH]$ will largely determine the reaction velocity, and at low concentrations of the alcohol, the dominant term will be $k_2^{\mathrm{II}}[HOCl]^2$. The first term of this equation represents the bimolecular attack of hypochlorous acid on the ethenoid centre, whilst the second is interpreted as the rate of formation of chlorine

monoxide by the equation $2HOCl = Cl_2O + H_2O$, the chlorine monoxide reacting with the alcohol as rapidly as it is formed.

A similar type of kinetic expression would provide a satisfactory explanation of the observations of Schilov, Kaniaev, and Otmennikova (*loc. cit.*) that the velocity of addition of hypochlorous acid to ethylene in aqueous solution conforms approximately to the equation $v = k_3[HOCl]^3$, where k_3 is not quite independent of the concentration of ethylene.

Since k_2' and k_2'' refer to the overall reaction and are unsatisfactory constants for indicating the specific rate, the initial velocity of the reaction was determined in subsequent work. Reasonable precision in this determination is possible if the time–titre values are plotted in such a way as to yield a linear or nearly linear graph. By substituting the known initial concentrations $[HOCl]_0$ and $[C_2H_4{\cdot}OH]_0$ and the measured initial velocity v_0 in equation (1), a series of simultaneous equations resulted, from which values of k_2^{I} and k_2^{II} were obtained. The results of this test of equation (1) are given in the four sections of Table VI, where concentrations are in mole $l.^{-1}$ and velocities in mole $l.^{-1}$ $min.^{-1}$.

TABLE VI.

$10^3[HOCl]_0$.	$10^3[C_2H_4{\cdot}OH]_0$.	10^6v_0, obs.	10^6v_0, calc.	$10^3[HOCl]_0$.	$10^3[C_2H_4{\cdot}OH]_0$.	10^6v_0, obs.	10^6v_0, calc.
1·95	1·0	6·3	6·4	2·00	3·0	13·3	13·3
1·98	2·0	10·0	9·8	2·00	4·0	16·6	16·6
1·92	2·5	11·0	11·0	1·95	5·0	19·3	19·3

k_2^{I} = 1·82, 1·52, 1·70, 1·61, 1·64; mean value, 1·66 l. $mole^{-1}$ $min.^{-1}$.
k_2^{II} = 8·00, 8·78, 8·35, 8·43, 8·18, 8·13; mean value, 8·31 l. $mole^{-1}$ $min.^{-1}$.

pH : 4·5.

2·54	0·8	8·8	9·1	2·54	1·6	13·4	13·1
2·54	1·2	11·5	11·1	2·54	2·0	14·8	15·2

k_2^{I} = 1·98 l. $mole^{-1}$ $min.^{-1}$; k_2^{II} = 7·88 l. $mole^{-1}$ $min.^{-1}$.

pH : 4·0.

3·99	0·8	19·3	19·7	3·90	1·6	23·9	23·4
3·99	1·2	22·3	22·0	3·88	2·0	25·0	25·4

k_2^{I} = 1·42 l. $mole^{-1}$ $min.^{-1}$; k_2^{II} = 9·56 l. $mole^{-1}$ $min.^{-1}$

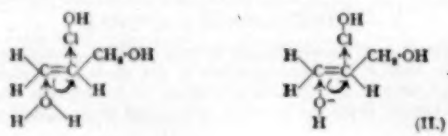
pH : 3·8.

4·78	0·8	27·8	28·2	4·76	1·6	32·8	32·9
4·78	1·2	31·4	30·7	4·78	2·0	35·2	35·6

k_2^{I} = 1·29 l. $mole^{-1}$ $min.^{-1}$; k_2^{II} = 10·21 l. $mole^{-1}$ $min.^{-1}$.

In each of these sections, the initial velocities v_0, calc., have been obtained by using the corresponding values of the two rate constants, k_2^{I} and k_2^{II}. The results given in the tables demonstrate that equation (1) provides a satisfactory representation of the kinetics of the reaction.

The results of experiments in which the pH of the reaction mixture varied appear to indicate that both k_2^{I} and k_2^{II} alter to some extent with pH, the former increasing with increasing concentration of hydroxyl ion, and the latter with increasing hydrogen-ion concentration. For pH's 3·8, 4·0, and 4·5, k_2^{I} has the values 1·29, 1·42, and 1·98, whilst k_2^{II} has the values 10·21, 9·56, and 7·88, respectively. The exact nature of the dependence of the two rate constants on pH necessitates an examination of the kinetics of the reaction in buffered solutions. However, the catalysis by hydrogen ion of the formation of chlorine monoxide from hypochlorous acid would not be unexpected, since the hydrolysis of other acid anhydrides (the reverse reaction) is catalysed by hydrogen ions (cf. hydrolysis of acetic anhydride, Orton and Jones, *J.*, 1912, **101**, 1708). The tendency of the specific rate of the direct reaction, k_2^{I}, to increase with increasing hydroxyl-ion concentration is also to be expected as the formation of chlorohydrin may be completed by either a water molecule (I) or a hydroxyl ion (II). The latter would conceivably provide an easier reaction path.



The fact that the term $k_3^{II}[HOCl]^2$ is independent of the concentration of the alcohol, necessitates, on the interpretation offered, that chloride monoxide is removed as rapidly as it is formed and it must, therefore, be much more highly reactive than hypochlorous acid. This would be expected from the potential ease of separation of positive chlorine from chlorine monoxide and from hypochlorous acid. The ratio of the ionisation constants of these two substances into positive chlorine is given by

$$\frac{[Cl^+][OCl^-]}{[Cl_2O]} \Big/ \frac{[Cl^+][OH^-]}{[HOCl]} = \frac{[HOCl]^2}{[Cl_2O]} \cdot \frac{[H^+][OCl^-]}{[HOCl]} \cdot \frac{1}{[H^+][OH^-]} = \frac{K_a}{K_{Cl_2O}K_w}$$

where K_{Cl_2O}, the equilibrium constant for the reaction $2HOCl \rightleftharpoons Cl_2O + H_2O$, has the approximate value 10^{-2} (Goldschmidt, *Ber.*, 1919, **52**, 753). Since K_a for hypochlorous acid is 4×10^{-8}, the calculated relative potential ease of ionisation of chlorine monoxide and hypochlorous acid to give positive chlorine is approximately 4×10^6, in harmony with the postulated high reactivity of chlorine monoxide.

Experimental.

Materials.—The allyl alcohol was B.D.H. reagent and was fractionated immediately before use in an all-glass apparatus; b. p. 96·5° (uncorr.)/753 mm.

Hypochlorous acid solutions were prepared by bubbling chlorine through a suspension of yellow mercuric oxide in distilled water. The acid solution was obtained by distillation of the resulting mixture under vacuum at as low a temperature as possible (not greater than 30°). The distillate was collected in a receiver cooled in ice and was stored over yellow mercuric oxide until required.

Kinetic Measurements.—All experiments were carried out at 25·00° ± 0·01°. The hypochlorous acid solution was prepared daily by centrifuging the stored solution and diluting the resulting liquid to a suitable strength with distilled water.

In all preliminary experiments, the reaction was carried out by placing the required amount of the stock allyl alcohol solution together with distilled water in the reaction flask. The reaction was started by adding the requisite volume of the hypochlorous acid solution. 10-Ml. samples of the reaction mixture were withdrawn at suitable intervals and run into 10 ml. of 2% potassium iodide solution acidified with 5 ml. of 5N-acetic acid, and the liberated iodine titrated with thiosulphate.

In later experiments, results of which are recorded in Table VI, the reaction was carried out by pouring simultaneously equal volumes of solutions of the two reactants into a suitable reaction flask, temperature equilibrium being maintained throughout.

The results of a typical experiment carried out using the latter method, are given in the following table; 10 ml. of approximately 0·05N-hypochlorous acid were diluted to 50 ml. in a standard flask. Similarly, 8 ml. of 0·2N-allyl alcohol were diluted to 50 ml., and the reaction started by mixing the two solutions so obtained.

$[HOCl]_0 = 4·76 \times 10^{-3}$ mole l.$^{-1}$, $[C_3H_5{\cdot}OH]_0 = 1·6 \times 10^{-3}$ mole l.$^{-1}$,

pH = 3·8. Temp. = 25·00° ± 0·01°.

Time (mins.)	0	1	2	3	4	5	6
Titre (ml. of N/250-$Na_2S_2O_3$)	23·82	22·22	20·76	19·38	18·16	17·07	16·08
$\log_{10}$ titre	1·377	1·347	1·317	1·287	1·259	1·232	1·206

For experiments in which the pH was measured, a sample of the reaction mixture was examined in a Macbeth direct-reading pH meter. The pH showed little or no variation during the reaction. The different pH values recorded in the last three sections of Table VI are undoubtedly due to the accumulation of small quantities of chloric acid in the stored hypochlorous acid solution through decomposition. Such traces of chloric acid are sufficient to depress the pH markedly but are scarcely detectable analytically. Further, the chloric acid does not appear to interfere with the course of the reaction except in so far as the pH is affected.

Determination of v_0.—To determine the initial velocity in each reaction mixture, it was necessary to find a suitable linear relationship between titre and time. It was found that the plot of $\log_{10}$ titre against time was satisfactory in this respect in the early stages of the reaction (up to 5 minutes). Extrapolation of the linear portion to zero time gave the value of the initial titre and hence the initial concentration of hypochlorous acid in the reaction mixture. The initial value quoted in the foregoing table was obtained in this way.

One of us (G. C. I.) acknowledges the generosity of the University of Tasmania, and the Engineering Board of Management, Hobart, in granting him twelve months' leave for study purposes.

University of Otago, Dunedin, New Zealand. [*Received, December 28th*, 1949.]

261. *The Kinetics of Chlorohydrin Formation. Part II. The Reaction between Hypochlorous Acid and Allyl Alcohol in the Presence of Sodium Acetate–Acetic Acid Buffers of Constant* pH.

By G. C. Israel.

The reaction between hypochlorous acid and allyl alcohol in aqueous solutions buffered by equal quantities of sodium acetate and acetic acid to pH 4·75 has been found to conform to the kinetic equation $v = k_3^{I}[HOCl][C_3H_5{\cdot}OH] + (k_3^{II} + k_3^{III}[HOAc])[HOCl]^2 + k_3^{III}[HOCl][HOAc]$. The various terms in this equation are interpreted as: k_3^{I}, the specific rate for direct addition of hypochlorous acid to allyl alcohol; k_3^{II} and k_3^{III}, the specific rates of formation of chlorine monoxide from hypochlorous acid in solution, the latter representing the catalytic effect of the acetic acid present; and k_3^{III}, the specific rate of formation of acetyl hypochlorite by the reaction $AcOH + HOCl \longrightarrow AcOCl + H_2O$.

In Part I (preceding paper) it was shown that the addition of hypochlorous acid to allyl alcohol in aqueous solution could be represented kinetically by the equation

$$v = k_3^{I}[HOCl][C_3H_5{\cdot}OH] + k_3^{II}[HOCl]^2$$

k_3^{I} being the specific rate for direct interaction between the two reactants, and k_3^{II} the specific rate of formation of chlorine monoxide from hypochlorous acid in solution. The chlorine monoxide so formed is probably a potentially better source of positive chlorine than is hypochlorous acid, and reacts readily with the ethenoid centre. The reaction is completed by addition of hydroxyl ions, possibly derived from water molecules, to the carbonium ion.

However, in Part I (*loc. cit.*) it was shown that the values of k_3^{I} and k_3^{II} may depend to some extent on the pH, and in order to avoid such variation, the reaction has now been investigated in the presence of equal quantities of sodium acetate and acetic acid. Since, for acetic acid, $K_a = 1{\cdot}770 \times 10^{-5}$ (Jeffery and Vogel, *J.*, **1932**, **2829**), the pH of all reaction mixtures was thus maintained at the value 4·75. All experiments were carried out at 25·00° ± 0·01°.

Preliminary experiments showed that the addition reaction is unaffected by the presence of a neutral salt such as potassium nitrate (cf. Schilov and Kaniaev, *Trans. Inst. Chem. Tech. Ivanovo*, **1935**, 19) but that the reaction velocity is markedly increased by the addition of a sodium acetate–acetic acid buffer and that acetic acid is not consumed during the reaction. Further, the addition of sodium acetate to the buffer mixture caused only a small increase in the reaction velocity, whereas additions of acetic acid caused considerable increase. Similar effects, due to the free acid of the buffer, have been observed in other reactions involving hypohalous acids (Mauger and Soper, *J.*, **1946**, **71**; Painter and Soper, *J.*, **1947**, **342**; Wilson and Soper, *J.*, **1949**, **3376**), and are attributed to the formation of highly reactive acyl hypohalite: $AcOH + HOX \longrightarrow AcOX + H_2O$.

In the present investigation, the initial velocity, v_0, was determined by using the method described in Part I (*loc. cit.*) for varying concentrations of hypochlorous acid, allyl alcohol, and acetic acid. Table I shows the variation in the initial velocity, v_0, as the concentration of allyl alcohol is altered. By analogy with the kinetic equation which was found to represent the rate of addition of hypochlorous acid to allyl alcohol in unbuffered solutions, it was assumed that the initial velocity conformed to an equation of the type

$$v_0 = k_3^{I}[HOCl]_0[C_3H_5{\cdot}OH]_0 + v_{res.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $v_{res.}$ is the residual (initial) velocity which is independent of the concentration of allyl alcohol but dependent on the concentrations of both hypochlorous acid and acetic acid. This assumption is verified by the constancy of the values of k_3^{I} and of $v_{res.}$.

Again, following the results obtained for the reaction in unbuffered solutions, it was assumed that the residual initial velocity, $v_{res.}$, conformed to the equation

$$v_{res.} = k_3^{II}[HOCl]_0^2 + k^{HOAc}[HOAc] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where k_3^{II} is a constant and k^{HOAc} is independent of the concentrations of allyl alcohol and acetic acid, but dependent on the concentration of hypochlorous acid. That equation (2) is substantially correct is clear from Fig. 1, in which the values of $v_{res.}$ have been obtained from the experimentally determined values of the initial velocity, v_0, by using equation (1), the value of k_3^{I} being taken as 2·0 l. mole^{-1} min.$^{-1}$. From the graphs, the values of k^{HOAc} derived from the gradients, and of $v_{res.}$ extrapolated to [HOAc] = 0 are shown in Table II. Such extrapolated values of $v_{res.}$ are equal to $k_3^{II}[HOCl]_0^2$, and hence, the derived values of k_3^{II} are also given in that table.

TABLE I.

10^3[HOCl]$_0$.	10^3[HOAc]$_0$ = 10^3[OAc$^-$]$_0$.	10^3[C_2H_4·OH]$_0$.	10^4v_0.	k_2^I (mean).	$10^4v_{max.}$	$10^4v_{max.}$ (mean).
2·07	1	0·5	9·29	2·03	7·29	7·35
		1·0	11·66		7·47	
		1·5	13·57		7·29	
		2·0	15·61		7·44	
4·03	1	0·8	27·5	2·11	21·7	20·7
		1·2	30·8		21·0	
		1·6	33·1		19·5	
		2·0	38·0		21·0	
3·83	3	0·8	41·0	1·93	35·1	35·1
		1·2	44·0		35·1	
		1·6	47·1		35·3	
		2·0	49·8		35·0	
3·84	4	0·8	49·3	1·85	43·6	43·6
		1·2	52·0		43·5	
		1·6	55·5		44·1	
		2·0	57·2		43·0	
4·02	5	0·8	60·2	1·74	54·6	54·7
		1·2	62·9		54·5	
		1·6	66·2		55·0	
		2·0	68·5		54·5	
4·69	2	0·4	39·9	2·23	35·7	36·2
		0·8	45·7		37·3	
		1·2	48·0		35·5	
		1·6	52·6		35·9	
		2·0	57·3		36·4	

Mean value of k_2^I over all experiments: 1·98 l. mole^{-1} min.$^{-1}$.

TABLE II.

10^3[HOCl]$_0$, mole l.$^{-1}$	1·95	2·07	2·92	3·93	4·91
10^3k^{HOAc}, min.$^{-1}$	3·4	3·9	5·6	8·6	10·9
$10^4v_{max.}$, mole l.$^{-1}$ min.$^{-1}$ (extrapolated)	3·0	3·5	6·6	11·6	21·4
k_2^{II}, l. mole^{-1} min.$^{-1}$	7·9	8·1	7·7	7·5	8·9

FIG. 1.

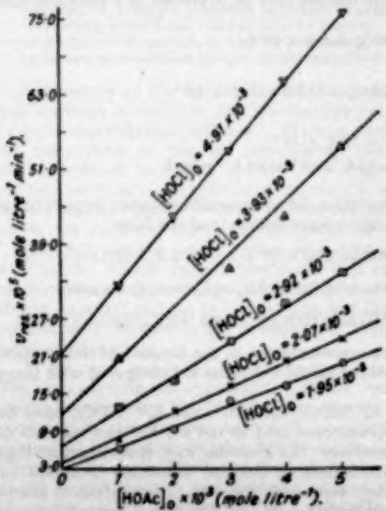
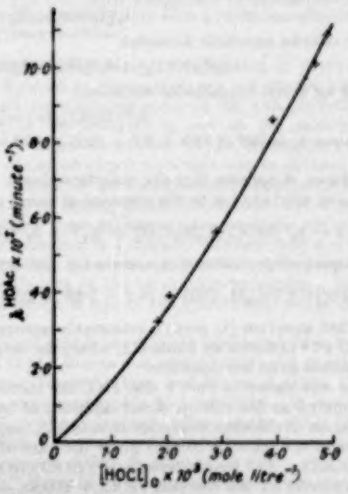


FIG. 2.



Whilst k_2^{II} is reasonably constant (mean value: 8·2 l. mole^{-1} min.$^{-1}$), k^{HOAc} may be expressed as a function of the concentration of hypochlorous acid by the equation

$$k^{HOAc} = k_2^{II}[HOCl]_0^2 + k_2^{III}[HOCl]_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

as may be seen from Fig. 2. This curve gives k_3^{III} as 14·5 l. mole^{-1} min.$^{-1}$, and k_3^{II} as 1·56 × 10^3 l.^{2} mole^{-2} min.$^{-1}$.

TABLE III.

10^3[HOCl]$_0$.	10^3[HOAc]$_0$.	10^3[C_3H_5·OH]$_0$.	10^4v_0. Calc.	Obs.	10^3[HOCl]$_0$.	10^3[HOAc]$_0$.	10^3[C_3H_5·OH]$_0$.	10^4v_0. Calc.	Obs.
1·95	1	1·0	10·4	10·2	3·84	4	0·8	50·1	49·3
	2	1·0	13·9	13·3		4	1·2	52·6*	52·0
	3	1·0	17·3	17·8		4	1·6	55·6	55·5
	4	1·0	20·7	20·2		4	2·0	58·7	57·2
	5	1·0	24·1	23·8					
					4·02	5	0·8	61·5	60·2
2·07	1	0·5	9·3	9·3		5	1·2	64·7	62·9
	1	1·0	11·4	11·7		5	1·6	68·0	66·2
	1	1·5	13·4	13·6		5	2·0	71·2	69·5
	1	2·0	15·5	15·6					
	2	1·0	15·0	15·6	4·01	10	0·8	102·8	100·2
	3	1·0	18·7	19·4		10	1·2	106·0	105·7
	4	1·0	22·5	23·2		10	1·6	109·2	109·3
	5	1·0	26·2	27·1		10	2·0	112·4	113·9
2·92	1	1·0	18·3	18·5	4·69	2	0·4	42·3	39·9
	2	1·0	24·0	22·8		2	0·8	46·1	45·7
	3	1·0	29·5	29·2		2	1·2	49·3	48·0
	4	1·0	35·0	35·3		2	1·6	53·1	52·6
	5	1·0	40·6	40·3		2	2·0	57·4	57·3
4·03	1	0·8	28·0	27·5	4·91	1	1·0	40·5	42·1
	1	1·2	31·3	30·8		2	1·0	51·3	53·2
	1	1·6	34·5	33·1		3	1·0	62·3	63·7
	1	2·0	37·7	38·0		4	1·0	73·1	74·8
						5	1·0	84·0	85·9
3·83	3	0·8	41·7	41·0					
	3	1·2	44·8	44·0					
	3	1·6	47·8	47·9					
	3	2·0	50·9	49·8					

* The relative contributions to the speed of the reaction may be of interest in a particular case. In this instance, for direct addition,

$$k_3^{I}[HOCl]_0[C_3H_5{\cdot}OH]_0 = 9{\cdot}2 \times 10^{-4},$$

for chlorine monoxide formation

$$k_3^{II}[HOCl]_0^2 + k_3^{II}[HOCl]_0^2[HOAc]_0 = (12{\cdot}0 + 9{\cdot}2) \times 10^{-4},$$

and for acetyl hypochlorite formation,

$$k_3^{III}[HOCl]_0[HOAc]_0 = 22{\cdot}2 \times 10^{-4};$$

whence $v_0 = (9{\cdot}2 + 12{\cdot}0 + 9{\cdot}2 + 22{\cdot}2) \times 10^{-4} = 52{\cdot}6 \times 10^{-4}$ mole l.$^{-1}$ min.$^{-1}$.

Hence, it appears that the complete kinetic equation for the reaction between hypochlorous acid and allyl alcohol in the presence of acetic acid–acetate buffers is of the form

$$v = k_3^{I}[HOCl][C_3H_5{\cdot}OH] + (k_3^{II} + k_3^{II}[HOAc])[HOCl]^2 + k_3^{III}[HOCl][HOAc] \quad . \quad (4)$$

For equal concentrations of acetate ion and acetic acid (pH 4·75), equation (4) becomes

$$v = 2{\cdot}0[HOCl][C_3H_5{\cdot}OH] + (8{\cdot}2 + 1{\cdot}56 \times 10^3[HOAc])[HOCl]^2 + 14{\cdot}5[HOCl][HOAc] \quad . \quad (5)$$

That equation (5) gives a reasonably accurate representation of the kinetics of the reaction at pH 4·75 is shown in Table III, where the measured initial velocities are compared with those calculated from the equation.

As was shown in Part I (*loc. cit.*), the terms $k_3^{I}[HOCl][C_3H_5{\cdot}OH]$ and $k_3^{II}[HOCl]^2$ may be interpreted as the rate of direct addition of hypochlorous acid to the alcohol and the rate of formation of chlorine monoxide in solution, respectively. In a similar way, it is suggested that the term $k_3^{II}[HOCl]^2[HOAc]$ gives the rate of formation of chlorine monoxide catalysed by acetic acid. The fourth term, $k_3^{III}[HOCl][HOAc]$, represents the rate of formation of acetyl hypochlorite by the reaction HOCl + HOAc ⟶ AcOCl + H_2O. The acetyl hypochlorite so formed is a potentially better source of positive chlorine than is hypochlorous acid.

It would appear that acetyl hypochlorite reacts much more rapidly than hypochlorous acid and is removed as rapidly as it is formed.

If this interpretation is correct, the specific rates of formation of chlorine monoxide, k_3^{II} and k_3^{II}, and of acetyl hypochlorite, k_3^{III}, should each be independent of the nature of the olefinic substance.

EXPERIMENTAL.

Materials.—The allyl alcohol was B.D.H. reagent, twice redistilled in an all-glass apparatus; b. p. 96·6—96·7° (uncorr.)/773 mm., n_D^{15} 1·4141. Hypochlorous acid solutions were obtained as described in Part I (*loc. cit.*). The sodium acetate–acetic acid buffer used was prepared by making an acetic acid solution of suitable strength from purified glacial acetic acid and partly neutralising it with carbonate-free sodium hydroxide solution.

Kinetic Measurements.—These have been described in Part I (*loc. cit.*). In most of the kinetic experiments, the required amount of the buffer was added to the solution of allyl alcohol, but no difference was observed when it was added instead to the hypochlorous acid solution.

The effect of neutral salt on the velocity of addition was examined by carrying out a series of reactions with constant concentrations of both allyl alcohol and hypochlorous acid and varying concentrations of potassium nitrate. No buffer was added in these experiments, the results of which are shown below.

$[HOCl]_0 = 2 \times 10^{-3}$ mole l.$^{-1}$; $[C_3H_5{\cdot}OH]_0 = 4 \times 10^{-3}$ mole l.$^{-1}$.

$10^2[KNO_3]$, mole l.$^{-1}$	0	1	3	5
$10^5 v_0$, mole l.$^{-1}$ min.$^{-1}$	4·40	4·46	4·47	4·47

The author acknowledges the many suggestions and helpful criticisms given by Professor F. G. Soper of the University of Otago, Dunedin, New Zealand, where this investigation was carried out, and also the valuable assistance of Mr. J. K. Martin in the early stages of this investigation.

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262. *The Constitution of Xylan from Esparto Grass* (Stipa tenacissima, *L.*).

By S. K. CHANDA, E. L. HIRST, J. K. N. JONES, and E. G. V. PERCIVAL.

A xylan containing no arabinose residues has been prepared from esparto grass. After the hydrolysis of its methylated derivative and the chromatographic separations of the products, both on paper strips and on a column of cellulose, it is concluded that the polysaccharide consists of a singly branched molecule containing 75 (±5) D-xylopyranose units, the single branching point being formed by a 1 : 3-union. This conclusion is supported by the results of oxidation with periodate, and by estimation of the reducing power with 3 : 5-dinitrosalicylic acid and of molecular weight by the osmotic-pressure method.

THE chemistry of the formation and inter-relations of the various components of plant cell-wall materials is complex, and the theories put forward in explanation are not always backed by rigid experimental evidence. These materials are probably some of the end products of the metabolism of the cell protoplasm, but the biochemistry is not as yet sufficiently well understood to enable one to follow stage by stage the process of the formation of the cell-wall materials. In general terms, the cell-wall carbohydrate materials can be divided into three classes—" pectin " which is removed by neutral or acid extraction, " hemicelluloses " which are removed from the remainder by various strengths of alkali, and the residual " cellulose." In the woody tissues of higher plants these substances are generally associated with lignin. Simple examination shows that each fraction is a complex mixture, and a critical examination of each of the individual polysaccharides is necessary, therefore, before one can obtain an exact picture of the amount and distribution of the total polysaccharides. In the present work we discuss the chemistry of xylan which is one of the main components of the hemicellulose group.

It has been known for some time that combined arabinose (6%) is associated with xylan. The early experiments appeared to indicate that the arabinose was present as an end group in a molecule comprising 18—20 xylopyranose residues (Haworth, Hirst, and Oliver, *J.*, 1934, 1917), occurring in the furanose form and, therefore, very susceptible to hydrolysis. It could be eliminated by hydrolysis with 0·005*N*-oxalic acid without seriously affecting the chain length (Bywater, Haworth, Hirst, and Peat, *J.*, 1937, 1983). It was found that fractional precipitation as the copper complex progressively reduced the total arabinose content of xylan, suggesting that the so-called " araboxylan " or " xyloaraban " might be, not a homogeneous polysaccharide, but a mixture of a true xylan with an araban of the type present in pectic materials.

The xylan was isolated from esparto holocellulose by extraction with dilute sodium hydroxide solution at room temperature, followed by acidification with acetic acid and precipitation with

acetone. After reprecipitation, a white product was obtained, similar in composition to the esparto xylans previously examined (Haworth, Hirst, and Oliver, *loc. cit.*; Bywater, Haworth, Hirst, and Peat, *loc. cit.*) in respect of the xylose (84%) and arabinose (7·5%) contents, although glucose (5·7%) was also found in the products of hydrolysis. These constituents were determined by quantitative paper chromatography (Flood, Hirst, and Jones, *J.*, 1948, 1679).

After several precipitations, as the copper complex, with Fehling's solution, followed by extraction with water to remove a soluble polyglucosan, a xylan was obtained which on hydrolysis gave neither glucose nor arabinose. The xylan, $[\alpha]_D$ −92° (*c*, 0·5 in 0·5*N*-sodium hydroxide), contained 0·5% of ash and 0·3% of lignin, and on hydrolysis gave D-xylose in 98% yield calculated by determination as furfuraldehyde phloroglucide or thiobarbiturate and in 95% yield as the crystalline dibenzylidene dimethyl acetal (Breddy and Jones, *J.*, 1945, 738). By filter-paper chromatography (Flood, Hirst, and Jones, *loc. cit.*) and determination by the Somogyi reagent, 97—98% of the xylan was accounted for as D-xylose, and no other sugars could be detected. A control experiment on the hydrolysis of β-methylxyloside under the experimental conditions used for the hydrolysis of the polysaccharide showed a loss of xylose amounting to 2%, so that the above results indicate a quantitative yield. Uronic acids were proved to be absent both by paper-chromatographic examination and by the naphtharesorcin test. Furthermore the yield (0·4%) of carbon dioxide obtained on heating the xylan with hydrochloric acid (19%) was comparable with that given by xylose itself under the same conditions.

The extraction of xylan and its delignification were carried out under mild conditions in order to minimise the possibility of degradation. During the purification by means of the copper complex no obvious signs of degradation were noted; in particular the value for the specific viscosity [$\eta_{sp.}/c$ = 10 in sodium hydroxide (0·5*N*.)] remained constant throughout the various stages.

By two series of five methylations, each with methyl sulphate and sodium hydroxide in an atmosphere of nitrogen, a methylated xylan was prepared, having $[\alpha]_D$ −85° (in chloroform) and containing 38% of methoxyl (Calc. for $C_7H_{14}O_4$: OMe, 38·7%). This was divided by fractionation using chloroform–light petroleum into two main fractions: (*A*) soluble in 3 : 7 chloroform–light petroleum and having OMe 38·6%, and (*B*) soluble in 3·5 : 6·5 chloroform–light petroleum and having OMe, 36·7%. On further methylation with methyl iodide and silver oxide (*B*) gave a product similar in properties to (*A*), including viscosity in *m*-cresol.

Paper-chromatographic examination (Hirst, Hough, and Jones, *J.*, 1949, 928) of the hydrolysates of the fully methylated samples described above indicated the presence of (*a*) 2 : 3 : 4-trimethyl xylose, (*b*) 2 : 3-dimethyl xylose, (*c*) monomethyl xylose, and (*d*) a trace of xylose. The sugars were identified by measuring the R_G values, confirmation being obtained by running standard sugars against the hydrolysate. The proportions of the various sugars in the hydrolysate were determined by hypoiodite oxidation after separation on a paper chromatogram, and were found to be (*a*) trimethyl xylopyranose 2·4—2·8% (molar) and (*c*) monomethyl xylose, 4·5—5·5%. The oxidation was carried out in sodium hydroxide–phosphate buffer (pH 11·4) (Ingles and Israel, *J.*, 1948, 810) and not in carbonate–bicarbonate buffer (pH 10·6), thereby removing the possibility of losing iodine through effervescence during the acidification of the solution. The reagent was found to oxidise stoicheiometrically the common aldoses and their methylated derivatives, in particular those of xylose. The chain length calculated on this result indicated one non-reducing end group per 36—41 residues.

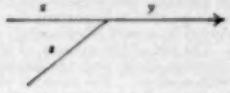
A similar result was also obtained when a quantity of methylated xylan hydrolysate was separated on a cellulose column (Hough, Jones, and Wadman, *J.*, 1949, 2511). The methylated xylan (6·2 g.) was converted first into the methylglycosides by 1% methanolic hydrogen chloride ($[\alpha]_D$ +71°, constant after 8 hours) and then into the free sugars by 0·5*N*-hydrochloric acid ($[\alpha]_D$ +55°, changing to +24° in 6 hours). The hydrolysate was concentrated to a syrup in each case and placed on the top of the column. It was developed with *n*-butanol–light petroleum (b. p. 100—120°) (3 : 7) saturated with water and containing 1% of ammonia, until the fully methylated pentose and 2 : 3-dimethyl xylose were removed. Monomethyl xylose did not travel sufficiently rapidly in this solvent, and the developing solution was therefore changed to *n*-butanol containing some water. An examination of the different fractions of the eluate showed a perfect separation of the sugars. The amount of pure 2 : 3 : 4-trimethyl xylose was 200 (±15) mg. The 2 : 3-dimethyl xylose weighed 6 g. and the amount of 2-methyl xylopyranose was 250 mg. Values calculated from the results of hypoiodite oxidations and determinations of specific rotation and methoxyl content were in agreement with these weights. Some 95% of the polysaccharide investigated was accounted for, a result much better than

could be expected by fractional distillation of the glycosides, a method inherently defective on account of losses by pyrolysis and incomplete separation. It was also proved that the yields both of the end group and of the partly methylated sugars could not be seriously affected by losses caused by demethylation during acid hydrolysis. A similar experiment carried out on chromatographically pure samples of 2 : 3 : 4-trimethyl and 2 : 3-dimethyl xylose showed (paper chromatography) that the former gave at most 1·5% of dimethyl and 0·4% of monomethyl xylose, whilst the latter gave only 0·3% of monomethyl derivative.

The trimethyl and the monomethyl xylose were both crystalline, and were identified as 2 : 3 : 4-trimethyl D-xylopyranose and 2-methyl D-xylopyranose respectively, confirmation being obtained by forming the anilides. *X*-Ray crystallographic examination (by courtesy of Dr. C. A. Beevers, Dewar Crystallographic Laboratory, Edinburgh University) of the trimethyl sugar showed it to be identical with trimethyl xylopyranose. The 2 : 3-dimethyl D-xylose was identified as its anilide, and as the lactone, amide, and *p*-bromophenylhydrazide of the corresponding 2 : 3-dimethyl xylonic acid.

The amount of trimethyl xylose obtained by quantitative separation of the methylated xylan hydrolysate on the cellulose column corresponded to 35 ± 3 residues per non-reducing end group. The molecular-weight determination of this sample by osmotic-pressure measurement (by courtesy of Professor H. W. Melville, F.R.S., of the University of Birmingham) gave a value of 11,000 (D.P. 70). Results of the same order were also obtained from the viscosities of the methylated (D.P. 86—90) and the acetylated xylan (D.P. 83). The viscosity in *m*-cresol was determined in an Ostwald viscometer, and molecular weights were calculated using the values $K_m = 12 \times 10^{-4}$ in the case of methylated xylan, and $K_m = 6{\cdot}3 \times 10^{-4}$ for the acetylated derivative. These constants are those valid for the corresponding cellulose derivatives, and it is realised that they may not be strictly applicable to a pentose polymer, particularly one for which it seems necessary to propose a branched structure. Nevertheless, the calculation of the molecular weights using these constants gave values closely similar to those obtained by osmotic-pressure measurement. The small discrepancy may be due to the branched structure, which, since only one branch point is involved may not seriously affect the results.

It is probable from these results that the xylan molecule comprises 70—80 β-D-xylopyranose units linked by 1 : 4-linkages (Haworth and Percival, *J.*, 1931, 2850) and terminated by one reducing and two non-reducing groups. The proportion of reducing groups in the xylan molecule will be discussed presently. On the above basis the xylan molecule will consist of a single branched chain which may be represented as follows :



$x + y + z = 75 \pm 5$

⟶ = Reducing group.

$X_{1,4}X_{1,4}X_{1,4}\cdots\cdots{}_{4}X_{1}\cdots{}_{4}X_{1,4}X_{1}$

$\vdots$

$X_{1,4}X_{1,4}\cdots\cdots{}_{4}X_{1}$

X = xylopyranose unit.

It follows that the fully methylated polysaccharide on hydrolysis should give one mole of monomethyl xylose per 2 moles of the end group. Just over a molar proportion of 2-methyl xylose was in fact separated and identified in the hydrolysate, indicating that the branching occurred through the position $C_{(2)}$ of a xylose residue in the 1 : 4-linked chain. The excess over the theoretical yield of the aforesaid monomethyl compound might well have arisen by demethylation of the 2 : 3-dimethyl xylose; the possibility of incomplete methylation in the first case, although improbable, cannot be excluded entirely.

This structure is in agreement with the results obtained (*a*) by determining the formic acid liberated from the end groups by periodate oxidation, and (*b*) by determination of the reducing group (several methods). One mole of formic acid will be liberated by periodate from each non-reducing terminal group in the molecule and 2 moles from the reducing end. In practice the amount of formic acid liberated was almost constant after 163 hours and corresponded to one mole per 20—21 residues, indicating 60 residues in an assumed straight chain or 80 on the branched structure proposed above. Very little xylose could be detected on hydrolysis of the fully oxidised xylan. This small residual amount of xylose probably came from the residue at the branching point in the xylan molecule which cannot be oxidised by the periodate. Just over one mole of periodate was necessary to oxidise each $C_5H_8O_4$ residue, in harmony with the presence of 1 : 4-linkages in the chains.

Estimation of the reducing group by colorimetric measurement of the reduction of 3 : 5-dinitrosalicylic acid to nitroaminosalicylic acid by the method of Meyer *et al.* (*Helv. Chim. Acta*, 1948, **31**, 103) gave a value of the order of one reducing group per 70—80 xylose residues. These authors used the absorption curve for maltose instead of glucose in their estimations of the chain length of amylose using the equation: D.P. = 2 × wt. of polyglucose/wt. of maltose. No corresponding disaccharide of xylose is known, but it was apparent from a comparison of the absorption curves for glucose and maltose that the chain length calculated from the latter is higher (nearly 30% higher when the colorimetric reading is not too low) than that obtained by using glucose for reference. As a first approximation, therefore, it may be assumed that a similar correction to the chain length of xylan will be necessary when it is calculated from the xylose curve, and we get, therefore, a value of 78—82 residues. A study of the nature of the three absorption curves for glucose, maltose, and xylose suggested that the absorption value of the hypothetical xylose disaccharide will approximate to that of glucose, and the chain length calculated on that assumption gives a value of 72—79 residues. It is difficult to make a definite decision on this point, but it is likely that the method gives an indication of the right order for the molecular weight.

Hypoiodite oxidation of the polysaccharide in a buffer medium (pH 10·6) indicated one reducing group per 48—50 residues. It is known that some over-oxidation occurs with this reagent, as is also apparent from the results of oxidation in the unbuffered medium, and it is very difficult to control the speed of the reaction. This method does not, therefore, give an accurate figure for the molecular size of the xylan, but it does show that the number of the residues per reducing group in the complex is not less than 50.

From the above considerations it seems justifiable to assign to the xylan from esparto grass a structure containing about 75 (±5) D-xylopyranose units joined by 1 : 4-β-linkages with a single branching point formed by a 1 : 3-union at some point as yet undetermined along the chain. A single-chain molecule is unacceptable in view of the evidence provided by the molecular weight, by osmotic pressure and by end-group determinations.

Experimental.

Preparation of Xylan from Esparto Grass.—The esparto grass [moisture, 9·3; ash, 3·6; lignin, 20·5 (Mahood and Cable, *Ind. Eng. Chem.*, 1922, **14**, 933); pentosan (as phloroglucide), 25·8; uronic anhydride, 3·1%], cut into pieces 3—4 cm. long, was extracted with benzene and methanol, to remove respectively the waxy and colouring materials, and milled to obtain a fibrous product, any powder being rejected. The material contained a high percentage of lignin (21—23%) and was delignified by Wise's method (*Ind. Eng. Chem., Anal.*, 1945, **17**, 63), slightly modified to suit the special conditions. The grass (100 g.) was suspended in water (5 l.) containing acetic acid (500 ml.) and sodium chlorite (500 g.). The solution was heated to 60° with occasional shaking and kept at that temperature for 1 minute. Sodium acetate (20 g.) was then added and the flask was transferred to a bath (thermostat) at 30° and kept at that temperature with occasional shaking for 24 hours. The pH of the solution (4·0) remained constant throughout the reaction. The mixture was filtered through cloth, and the fibrous residues were washed with ice-cold water, to remove the acid, and then with acetone. The product was dried in the air, a white fibrous holocellulose (moisture, 3·5; ash, 1·9; lignin, 2·4; pentosans, 30·2; uronic anhydride, 3·4%) being obtained (70—75 g.). The small amount of lignin did not, however, interfere with the xylan preparation since it could be left almost completely in the acetone solution during the precipitation of the xylan (see below). A second treatment by sodium chlorite removed the lignin completely but there was considerable degradation of the less resistant carbohydrate material.

The xylan was extracted from the holocellulose (100 g.) by rolling it for 24 hours in a "Kilner" jar containing glass marbles and sodium hydroxide solution (2 l.; 4%), the slurry was centrifuged and the crude xylan precipitated with acetone after acidification with acetic acid. This operation was repeated on the residual solid. The small amount of lignin dissolved in the alkali was left in the acetone solution, as indicated by the brown colour. The crude xylan was collected on the centrifuge, and the precipitate was washed with acetone–water (1 : 1) to remove the acid, followed by alcohol of increasing concentration, and finally with ether. The solid was dried in the air till most of the ether had evaporated, whereafter the xylan (27—28 g.) could be powdered and then dried over phosphoric oxide in a vacuum desiccator. The product, $[\alpha]_D$ −91° (*c*, 0·5 in 0·5*N*-sodium hydroxide) was light brown but, after one or two reprecipitations, became colourless; this was xylan I (moisture, 1·2; ash, 0·58; lignin, 0·3; pentosans, 96·0; uronic anhydride, 0·4%). Chromatographic examination (Flood, Hirst, and Jones, *loc. cit.*) of the hydrolysate showed that the polysaccharide contained arabinose (7·5%) and glucose (5·65%) along with xylose (84%).

Purification of Xylan.—The crude xylan (20 g.) was dissolved in sodium hydroxide (1·5 l.; 4%), and the solution treated with equal volumes of freshly prepared Fehling's solution whereupon the copper complex was precipitated. A little acetone was added for quick settling of the precipitate. The top, clear liquid was decanted off, and the solution filtered through mercerised muslin. The precipitate was suspended in water (1 l.) by vigorous stirring. Cold hydrochloric acid (2*N*.) was then added carefully to decompose the copper complex, a clear or occasionally slightly opalescent polysaccharide solution being obtained. The acidity of the solution was never allowed to exceed *N*. The polysaccharide was precipitated with acetone, avoiding excess, to give a white flocculent precipitate.

The solution was centrifuged and the precipitate washed with slightly acidified acetone–water (60 : 40), to remove the copper completely, and then with the solvent mixture to remove the acid, and finally with alcohol and ether. It was dried over phosphoric oxide in a desiccator.

The polysaccharide was then suspended in water (500 c.c.) and shaken overnight to separate the water-soluble fraction. The insoluble fraction obtained on centrifuging was dried as before (xylan II). The glucose and arabinose in the insoluble fraction were progressively removed by such purifications. Usually 2—3 purifications as the copper complex were necessary to obtain from old specimens of esparto grass a xylan free from glucose and arabinose (yield, 80—85%). Some 5—6 such purifications were necessary to obtain pure xylan (xylan III) from a green and relatively fresh sample of the grass (yield, 60—70%). An attempt to fractionate the pure xylan by precipitation with glacial acetic acid was unsuccessful as the polysaccharide was completely precipitated by the acid. The polysaccharide, however, did not seem to be degraded since the same value for the viscosity in N-sodium hydroxide was obtained for xylan at different stages of purification ($\eta_{sp.}/c = 10{\cdot}0$, where c is in Staudinger units). Xylan III had $[\alpha]_D^{20}$ −92° (*c*, 0·5 in 0·5N-sodium hydroxide) (ash, 0·5; lignin, 0·3; pentosan, 98%). It gave 95% of the theoretical amount of xylose after hydrolysis [estimated as xylose dibenzylidene dimethyl acetal by the Breddy–Jones reagent (*loc. cit.*), using the equation $y = 0{\cdot}5175x + 0{\cdot}0457$ where y is the weight of xylose and x the weight of the derivative]. Filter-paper chromatographic estimation of the xylose (no other sugar could be detected) obtained on hydrolysis with 0·5N-sulphuric acid, with Somogyi's copper reagent, accounted for 97—98% of xylan. A control experiment of the hydrolysis of β-methylxyloside under identical conditions indicated that nearly 2% of the xylose was destroyed during hydrolysis. The polysaccharide, therefore, consisted of xylose only and was obtained in a very pure state (98—99%). No uronic acid could be detected in the pure polysaccharide either by paper chromatogram or by the naphtharesorcinol test.

Methylation of Xylan.—Xylan III (18 g.) was suspended in water (100 c.c.) in a three-necked round-bottomed flask and allowed to swell overnight. The air was then displaced by nitrogen, a gentle stream of the gas being maintained throughout. Sodium hydroxide [200 c.c.; 40% (by wt. throughout)] was then added with vigorous mechanical stirring, and the solution was stirred for 4 hours. Methyl sulphate (180 c.c.) was then added dropwise during 6—8 hours, the flask being cooled in ice and water. After overnight stirring the reaction was completed by heating in a water-bath for 1 hour. The mixture was cooled and treated with sodium hydroxide (300 c.c.; 40%) followed by methyl sulphate (180 c.c.) as before, and this process was repeated 4 times at room temperature in nitrogen; cooling in ice was unnecessary after the first methylation. Before the fifth methylation acetone (200 c.c.) was added; it was removed by distillation on completion of the methylation. The mixture was then cooled and treated with sulphuric acid (0·5N.) until it was faintly alkaline (pH 8); it was then boiled with water, whereupon the precipitated sodium sulphate dissolved and the methylated xylan separated. The product was filtered hot through cloth, washed with hot water, and dried at 95°/15 mm. (Found: OMe, 32·2%). The aqueous solution and aqueous washings were extracted with chloroform, the solvent was removed, and the product added to the main bulk. The partly methylated xylan was dissolved in aqueous acetone (80%), and then treated with sodium hydroxide (300 c.c.; 40%) for 2 hours with stirring under nitrogen, followed by methyl sulphate as before. A second series of five methylations was carried out to give methylated xylan (20·2 g.), $[\alpha]_D^{20}$ −83° (*c*, 0·8 in chloroform) (Found: OMe, 36·4%).

Fractionation of Methylated Xylan.—The methylated xylan (20 g.) was treated with 300 c.c. (in two batches of equal volume) of purified light petroleum (b. p. 60—65°)–chloroform, the amount of the latter solvent in the mixture being increased in stages. For each extraction the mixture was boiled gently in a water-bath for 2 hours, the insoluble material allowed to settle, and the clear liquid decanted. The solvent was then removed under diminished pressure and the residue dried at 90—95°/15 mm. over phosphoric oxide to constant weight. The results are collected in Table I.

TABLE I.

Fraction.	Solvent, $CHCl_3$–light petroleum.	Yield, %.	Sulphated ash, %.	OMe, %.	$[\alpha]_D^{20}$.
1	0 : 100	0·6	Nil	1·5	−3°
2	10 : 90	0·9	0·04	4·2	−7
3	15 : 85	0·25	0·09	18·5	−26·5
4	20 : 80	0·4	0·11	22·0	−33
5	25 : 75	0·4	0·11	38·9	−83
6	30 : 70	41·3	0·2	37·9	−85
7	35 : 65	37	1·4	36·7	−84·5
8	Residue	15·9	6·2	34·8	—

Fraction 7 was treated with methyl iodide (200 c.c.) and silver oxide (100 g.), and after the usual treatment had OMe, 38%. The fraction was then completely soluble in 3 : 7 chloroform–light petroleum. Fractionation was carried out as before (Table II).

TABLE II.

Fraction.	Solvent, $CHCl_3$–light petroleum.	Yield, %.	Sulphated ash, %.	OMe, %.	$[\alpha]_D^{20}$.
7A	0 : 100	0·4	—	Nil	Nil
7B	15 : 85	0·3	Nil	25·0	−42°
7C	20 : 80	0·15	—	37·5	−81
7D	25 : 75	7·3	0·14	38·4	−85
7E	30 : 70	91·6	0·37	38·6	−85·5

Measurements of viscosity (see below) and other analytical data showed fractions 6 and 7E to be identical (Found: C, 52·5; H, 7·7. Calc. for $C_7H_{12}O_6$: C, 52·5; H, 7·5%).

Acetylation of Xylan.—Xylan (3·5 g.) was warmed with pyridine (150 c.c.) at 70° for 2 hours. After the mixture had been cooled to 15° acetic anhydride (40 c.c.) was added dropwise with shaking and the flask kept in the dark for 3 days with occasional stirring. The contents were then poured into water and the insoluble product was separated at the centrifuge, washed with water, alcohol, and ether and dried at room temperature over phosphoric oxide (Found: $CH_3{\cdot}CO$, 38·7%. Calc. for $C_9H_{14}O_6$: $CH_3{\cdot}CO$, 39·8%).

A second acetylation of this material gave a product (3·4 g.) with the theoretical acetyl content. The xylan acetate was insoluble in methanol, ethanol, acetone, or chloroform; it was soluble to some extent in pyridine and chloroform–ethanol (9 : 1) and had $[\alpha]_D^{20}$ −155° (*c*, 1·0 in *m*-cresol).

Viscosity Determination of Xylan and its Derivatives.—The viscosities of xylan in 0·5N-sodium hydroxide and its derivatives in *m*-cresol were measured in an Ostwald viscometer at 20° (Table III).

TABLE III.

Derivative.	Sample.	*c*.	Average time of flow in secs., solution.	solvent.	η_{sp}/c.	*M*.	D.P.
Xylan	Xylan I	0·1272	671·5	293	10·16	—	—
	Xylan II	0·1246	657	,,	10·02	—	—
	Xylan III	0·1363	684	,,	9·8	—	—
Acetylated xylan	Insoluble fraction	0·046	760	501	11·24	17,840	83
Methylated xylan	6	0·126	1541	,,	16·47	13,720	86
	7E	0·1356	1694	,,	17·56	14,630	91
	5	0·1323	1096	,,	8·97	7,474	47
	7D	0·1414	1111	,,	8·61	7,174	45

Molecular weights were calculated for the acetyl and methyl derivatives from the equation $\eta_{sp} = K_m Mc$, were *c* is concentration in g.-mol. of repeating units per litre. K_m for acetate $6·3 \times 10^{-4}$ and K_m for the methylated xylan 12×10^{-4} (*i.e.*, the constants applied to the corresponding cellulose derivatives; Staudinger and Reinecke, *Annalen*, 1938, **535**, 47).

A determination, carried out through the kindness of Professor H. W. Melville, F.R.S., of the molecular weight of methylated xylan (6) gave a value of 11,000 (D.P. 70).

Hydrolysis of Methylated Xylan and Separation of Methylated Xyloses.

(a) *By Paper Chromatography.*—The polysaccharide (100 mg.) was treated with methanolic hydrogen chloride (5 c.c.; 1%) in a sealed tube at 100° for 7—8 hours. After careful removal of the solvent, the residual syrup was hydrolysed for 6—8 hours with hydrochloric acid (10 c.c.; 0·5N.), neutralised with silver carbonate, and filtered, and silver was then removed from the filtrate by hydrogen sulphide and basic or acidic ions by " Deacidite B " and " Zeocarb H1 ". The clear solution was concentrated to a thin syrup at 35°/15 mm. Examination on the paper chromatogram with butanol–ethanol–water showed, on development with aniline oxalate, three distinct spots corresponding to a trimethyl pentose (R_0 0·94—0·95), 2 : 3-dimethyl xylose (R_0 0·74—0·76), and monomethyl xylose (R_0 0·38—0·41), together with a trace of xylose.

The method of Hirst, Hough, and Jones (*J.*, 1949, 928) for the estimation of methylated sugars by alkaline hypoiodite after separation on the paper chromatogram was modified by the use of a sodium hydroxide–phosphate buffer (pH 11·40) (Ingles and Israel, *J.*, 1948, 810), the method being shown (Table IV) to be applicable to the methylated sugars concerned. A known sugar solution (5 c.c.) was

TABLE IV.

Sample.	Weight, mg.	Weight, found, mg.	Recovery, %.	Sample.	Weight, mg.	Weight, found, mg.	Recovery, %.
2 : 3 : 4-Trimethyl xylose	0·215	0·213	99·1	Xylose	0·501	0·496	99·0
	0·430	0·426	99·1		1·002	0·997	99·5
	1·073	1·080	100·6		2·506	2·428	97·0
	2·146	1·990	92·7				
				Ribose	0·612	0·604	98·7
2 : 3-Dimethyl xylose	0·395	0·378	95·7		1·224	1·214	99·2
	0·988	0·966	97·8		3·060	2·907	95·0
	1·977	1·898	96·0				
				Rhamnose (hydrate)	0·559	0·494	88·4
2-Methyl xylose	1·230	1·214	98·7		1·118	0·961	86·0
	2·310	2·267	99·0		2·236	1·491	66·6
					2·795	1·689	60·4

treated with iodine (1 c.c.; 0·1N.) measured from an " Agla " micrometer syringe (in two batches), followed by 2 c.c. of the buffer (25 c.c. of 0·1N-disodium hydrogen phosphate and 8·67 c.c. of 0·1N-sodium hydroxide, diluted to 50 c.c.) into a " Quickfit " boiling tube, which was then quickly closed with a stopper moistened with 10% potassium iodide solution. The tube was kept in a cool, dark place for 6 hours, the stopper washed with water, and the solution acidified with sulphuric acid (2 c.c.; 2N.) and titrated with sodium thiosulphate (0·01N.). A blank was run concurrently.

It will be observed that, with the exception of rhamnose, the oxidation is practically stoicheiometric at low concentrations of sugars.

Methylated xylan (50 mg.) was hydrolysed as described above. Heavy spotting was necessary to determine the end group and a wide paper (21 cm.) was used, and the blank paper cut from the same sheet was hung from the opposite side of the trough. The filter-paper strips containing the sugars were extracted for 45 minutes with 5 c.c. of water contained in a boiling tube, cooled to room temperature, and analysed by the above method (see Table V). For the estimation of the dimethyl xylose the quantities of reagents was increased tenfold.

TABLE V.

Sugar.	Wt., mg.	Molar composition, %.	Sugar.	Wt., mg.	Molar composition, %.
Sample 6.			*Sample* 7*E*.		
2 : 3 : 4-Trimethyl xylose	0·26 0·28	2·5 2·8	2 : 3 : 4-Trimethyl xylose	0·20 0·19	2·4 2·7
2 : 3-Dimethyl xylose	8·64 8·57	91·5 91·7	2 : 3-Dimethyl xylose	7·10 5·97	92·1 91·5
2-Methyl xylose	0·49 0·44	5·5 5·0	2-Methyl xylose	0·32 0·28	4·5 4·7
Xylose	0·03 0·03	0·4 0·3	Xylose	0·06 0·06	0·9 1·0

These results indicate one reducing group per 36—41 xylose units.

(b) *By the Cellulose Column.*—Methylated xylan (6·2 g.) was boiled gently on a water-bath with methanolic hydrogen chloride (620 c.c.; 1%), the following rotations being observed: $[\alpha]_D^{\infty}$ +4° (1 hr.), 14° (2 hrs.), 20° (3 hrs.), 35° (4 hrs.), 51° (5 hrs.), 60° (6 hrs.), 68° (7 hrs.), 71° (8 hrs., constant). The solution was then cooled in ice–salt, and the acid neutralised by the addition of a dry ethereal solution of diazomethane. The solution was then concentrated to a syrup, which was dissolved in ether, filtered, concentrated, and heated at 40°/15 mm., to give a syrup (7·43 g.) which was hydrolysed at 95—100° with hydrochloric acid (310 c.c.; 0·5*N*.) and then had $[\alpha]_D^{\infty}$ +55° ⟶ +24·2° (6 hours, constant). The acid solution was neutralised with silver carbonate (previously triturated with water) and filtered, and silver was then removed with hydrogen sulphide. The solution was filtered through washed charcoal and concentrated to a syrup (7·0 g.) at 40°/15 mm.

A column of powdered cellulose (60 × 4 cm.) was prepared, washed, and tested as described by Hough, Jones, and Wadman (*J.*, 1949, 2511). The solvent selected for the operation after a preliminary trial with butanol–water was light petroleum (b. p. 100—120°)–*n*-butanol (7 : 3), saturated with water and containing 1% of ammonia. The above syrup was then dissolved in the minimum volume of the solvent for dissolution, added dropwise to the top of the column and allowed to soak in. A thin layer of cotton wool was then placed on the top of the column, followed by 100 c.c. of the solvent; the column was then left overnight. The reservoir was filled with solvent and the column developed by using the automatic device for changing the receiver every 5 minutes. 1 C.c. of the eluate from every tenth tube was concentrated on a watch-glass over a water-bath, and small spots were placed in chronological order along the starting line of filter-paper chromatogram and separated in the usual way. The residues on the watch-glasses were dissolved in acetone and transferred quantitatively to the respective tubes. On development of the paper a picture of the distribution of the sugars was obtained. Trimethyl xylose was completely separated between tubes 50 and 70, after a gap of 20 tubes dimethyl xylose appeared (90—240), and no sugars were eluted between tubes 240 and 500. At the 500th tube the solvent was changed to *n*-butanol, monomethyl xylose being collected between tubes 650 and 710. The column was then washed with water to obtain the trace of xylose known to be present and any residue remaining at the top of the column. The tubes were then grouped, the solvent was removed at 35°/15 mm., and the residue dissolved in water and filtered through charcoal to remove waxy impurities. After further concentration and drying by the addition of methanol and distillation, the following fractions were obtained: (1) trimethyl pentose (0·272 g.); (2) dimethyl pentose (6·03 g.); (3) monomethyl pentose (0·265 g.); and (4) xylose (0·06 g.).

Examination of the fractions. Fraction (1). Partial crystallisation took place gradually. The crystals (109 mg.) were separated on a tile and washed (53·6 mg.), the tile was extracted with chloroform, and the extract and washings were evaporated. A small quantity of material insoluble in methanol was removed, and two further crops of crystals (44·4 mg.) were removed. The residual syrup (136·3 mg.) was twice purified from light petroleum containing a trace of butanol, and a small insoluble residue rejected. The syrup eventually obtained (110 mg.) crystallised completely in one week (purity by hypoiodite oxidation 93—94%) and had $[\alpha]_D^{\beta}$ +20·3° (*c*, 1·1 in water), m. p. 87° raised to 90° on recrystallisation from ether (Found: OMe, 46%). The crystals (98 mg.) obtained from the first three batches had m. p. 89—90°, not depressed on admixture with trimethyl D-xylopyranose. Hypoiodite oxidation indicated 100% purity (Found: C, 50·1; H, 8·3; OMe, 48·5. Calc. for $C_8H_{16}O_5$: C, 50·0; H, 8·3; OMe, 48·4%).

Examination by the *X*-ray powder photograph method, by the kindness of Dr. C. A. Beevers, showed the substance to be 2 : 3 : 4-trimethyl xylose. The derived anilide had m. p. 102° alone or in admixture with an authentic specimen (Laidlaw and Percival, *J.*, 1949, 1600) (Found: C, 62·7; H, 7·8; N, 5·1; OMe, 34·9. Calc. for $C_{14}H_{21}O_4N$: C, 62·9; H, 7·8; N, 5·2; OMe, 34·8%).

The total quantity of trimethyl D-xylopyranose obtained was 210 (±15) mg., corresponding to one end group in 35 ± 3 residues.

The small quantity of insoluble residue obtained during the crystallisations was treated with water, and the concentrated filtrate examined chromatographically. No reducing sugars were detected.

Fraction (2). The syrup (6·03 g.) had $[\alpha]_D^{18}$ +23° (*c*, 2·4 in water), n_D^{18} 1·4770 (Found: OMe, 34·9. Calc. for $C_7H_{14}O_6$: OMe, 34·8%). The purity by the hypoiodite method was 98%. The derived lactone had $[\alpha]_D^{18}$ +97°, falling to +82·5° (720 hours, constant; *c*, 1·0 in water), n_D^{18} 1·4640 (Found: OMe, 34·7. Calc. for $C_7H_{12}O_6$: OMe, 35·2%).

The lactone was treated with methanolic ammonia to give 2 : 3-dimethyl D-xylonamide in theoretical yield, m. p. 134° alone or admixed with an authentic specimen, $[\alpha]_D^{18}$ +49° (*c*, 0·8 in water) (Found: C, 43·8; H, 7·9; N, 7·9; OMe, 32·0. Calc. for $C_7H_{15}O_5N$: C, 43·5; H, 7·7; N, 7·25; OMe, 32·1%).

Treatment in ether with *p*-bromophenylhydrazine gave 2 : 3-dimethyl D-xylono-*p*-bromophenylhydrazide (83%), m. p. 150° alone or admixed with an authentic specimen (Found: C, 43·1; H, 5·4; N, 7·75; Br, 21·8; OMe, 16·1. Calc. for $C_{13}H_{19}O_5N_2Br$: C, 43·0; H, 5·3; Br, 22·1; OMe, 17·1%).

Fraction (2) was converted into the anilide, m. p. 145° (alone or admixed with authentic 2 : 3-dimethyl D-xylose anilide), $[\alpha]_D^{18}$ +190° (*c*, 1·2 in ethyl acetate; const. for 24 hours), +118° (5 minutes), +96° (10 minutes), +80° (25 minutes), +75° (45 minutes, constant) [*c*, 0·9 in ethyl acetate containing acetic acid (5% v/v)] (Found: C, 61·6; H, 7·5; N, 5·7; OMe, 24·3. Calc. for $C_{13}H_{19}O_5N$: C, 61·6; H, 7·6; N, 5·5; OMe, 24·5%). Fraction (2) was, therefore, entirely 2 : 3-dimethyl D-xylose.

Fraction (3). The syrup (265 mg.) crystallised almost completely on inoculation with 2-methyl D-xylose. Direct comparison against authentic samples of 2- and 3-methyl xylose on the filter-paper chromatogram showed both crystals and adhering syrup to correspond to the former sugar. Washing with hot methanol gave 2-methyl β-D-xylose (152 mg.), m. p. 134° alone or in admixture with an authentic specimen, $[\alpha]_D^{18}$ +5° (10 minutes), 20° (30 minutes), 30° (2 hours), 34·5° (3 hours, constant) (*c*, 1·0 in water). Hypoiodite oxidation indicated a purity of 97% (Found: C, 43·9; H, 7·4; OMe, 18·5. Calc. for $C_6H_{12}O_5$: C, 43·9; H, 7·3; OMe, 18·9%). The syrup (111 mg.) recovered from the washings had $[\alpha]_D^{18}$ +32·4° (*c*, 1·1 in water) (Found: OMe, 18·3%). Hypoiodite oxidation indicated 96% monomethyl xylose, and the syrup crystallised almost completely when kept for a week, to give 2-methyl xylose, m. p. 134°.

Conversion into the anilide gave a product, m. p. 125° alone or admixed with 2-methyl D-xylose anilide (Found: C, 59·6; H, 7·1; N, 5·8; OMe, 13·1. Calc. for $C_{12}H_{17}O_4N$: C, 60·2; H, 7·1; N, 5·85; OMe, 13·0%).

Fraction (4). The semi-solid syrup (60 mg.) had $[\alpha]_D^{18}$ +12·5° (*c*, 3·0 in water) and was shown by filter-paper chromatography to contain xylose only, the amount calculated from the rotation being *ca.* 40 mg.

The Partial Demethylation of 2 : 3 : 4-*Trimethyl and* 2 : 3-*Dimethyl Xylose.*—Specimens of the appropriate sugars (100 mg.) were treated with methanolic hydrogen chloride (20 c.c.; 1%) for 8 hours, followed by aqueous hydrochloric acid (20 c.c.; 0·8N.) for 8—10 hours, under the conditions used for the hydrolysis of methylated xylan. The sugars were isolated in the usual way, dissolved in acetone, filtered to remove inorganic material, concentrated, and dried. The various sugars present were estimated on the paper chromatogram with buffered hypoiodite as described previously; 2—3 larger papers were needed to obtain sufficient of the demethylated sugars for estimation. The results are collected in the following table.

	0·01N-$Na_2S_2O_3$, c.c.		Methylated sugar, %.	
2 : 3 : 4-*Trimethyl Xylose.*				
Trimethyl xylose ...	23·83;	25·08	98;	98
Dimethyl xylose ...	0·38;	0·40	1·6;	1·6
Monomethyl xylose	0·09;	0·10	0·4;	0·4
2 : 3-*Dimethyl Xylose.*				
Dimethyl xylose ...	45·8;	46·06	99;	99
Monomethyl xylose	0·11;	0·24	0·14;	0·30

Other Experiments.

Periodate Oxidation of Xylan.—(1) *Determination of formic acid released.* The method of Halsall, Hirst, and Jones (*J.*, 1947, 1399, 1427) was used as modified below. Dry xylan (100 mg.) was weighed into each of a number of 50-c.c. stoppered bottles and treated with potassium chloride solution (5 c.c.; 16%), followed by sodium metaperiodate (10 c.c.; 0·083M.) and water (10 c.c.). Blanks were also started. The bottles were shaken continuously in the dark. Bottles were removed at intervals, the contents centrifuged, and 20 c.c. of the clear solution treated with ethylene glycol (1 c.c.) and titrated with sodium hydroxide solution (0·01N.) from a micro-burette (methyl-red). The alkali required for blank experiments (20 c.c.) was small (0·03 c.c.) and did not vary with time. A suspension of the xylan in water was neutral to methyl-red. The following results [moles ($\times 10^3$) of $H{\cdot}CO_2H$ per $C_5H_{10}O_5$ unit] were obtained: 1 hour, 0·17; 3 hours, 0·65; 73 hours, 4·4; 115 hours, 4·6; 163 hours, 4·8; 190 hours, 4·85; 235 hours, 4·9; 332 hours, 5·1. The amount of formic acid liberated was practically constant after 163 hours, corresponding to 1 mole per 20—21 xylose residues.

(2) *Uptake of periodate.* Batches (100 mg.) of xylan were shaken in the dark with sodium metaperiodate solution (25 c.c.; 0·25M.), the rotation becoming strongly positive. Samples were taken at intervals of 24 hours and diluted to 250 c.c. The amount of periodate consumed (per $C_5H_8O_4$ unit) was determined (Fleury and Lange, *J. Pharm. Chim.*, 1933, **8**, **17**, 107, 196): 0·96 (24 hours); 1·15 (48 hours); 1·28 (72 hours). The completely oxidised solution in a Cellophane bag was then dialysed against tap water until free from inorganic ions, concentrated at 35°/15 mm. to 1—2 c.c., and hydrolysed at 100° in a sealed tube with concentrated sulphuric acid (0·04 c.c.). After neutralisation with barium carbonate, examination on the filter-paper chromatogram indicated the presence of a trace of xylose.

The Reducing Power of Xylan.—(1) *Hypoiodite oxidation.* The polysaccharide (100 mg.) in water (10 c.c.) was treated with sodium hydroxide (10 c.c.; 2N.), followed by iodine (10 c.c.; 0·1N.). After two batches had been kept in the dark for 3 hours and 16 hours respectively, the solutions were acidified with sulphuric acid (25 c.c.; 2N.), and the regenerated iodine was titrated with sodium thiosulphate. Blanks were run concurrently. The results corresponded to one reducing group per 43—47 xylose residues. In another experiment the oxidation was conducted as before (3 hours) with the equivalent

of 40 c.c. of 0·1N-sodium hydroxide and 20 c.c. of 0·1N-iodine buffered with sodium carbonate (0·2M.)–sodium hydrogen carbonate (0·2M.) solution (5 c.c.). Excess of iodine was titrated after acidification, care being taken to lose no iodine during effervescence, giving a value of one reducing group per 48—50 xylose units.

(2) *Colorimetric method.* Meyer's method (*Helv. Chim. Acta*, 1948, **31**, 103) was used. Standard curves were constructed for maltose (Meyer, *loc. cit.*) and for glucose and xylose, by treating known amounts of the sugars (0·1—2 mg.) with 3 : 5-dinitrosalicylic acid (1 c.c.; 1·5%) and sodium hydroxide (1 c.c.; 6N.) at 65° for 30 minutes, cooling, and diluting to 25 c.c. The solution thus obtained was compared with a blank in a "Spekker" photoelectric absorptiometer using the 1-cm. cell and filter 604 (see Table VI).

TABLE VI.

Sugar.	mg./25 c.c.	G.-mol./25 c.c. × 10^6.	Log I/I_0.	Sugar.	mg./25 c.c.	G.-mol./25 c.c. × 10^6.	Log I/I_0.	Sugar.	mg./25 c.c.	G.-mol./25 c.c. × 10^6.	Log I/I_0.
Xylose	0·2	1·33	0·007	Glucose	0·2	1·11	0·005	Maltose	0·2	0·55	0·002
	0·3	2·0	0·016		0·3	1·66	0·015		0·5	1·46	0·020
	0·4	2·66	0·026		0·4	2·22	0·028		0·75	2·19	0·050
	0·5	3·33	0·053		0·5	2·77	0·046		1·0	2·92	0·091
	0·6	4·0	0·073		0·6	3·33	0·065		1·2	3·5	0·131
	0·7	4·66	0·102		0·7	3·88	0·094		1·5	4·38	0·197
	0·8	5·33	0·128		0·8	4·44	0·125		1·8	5·26	0·244
	0·9	5·99	0·164		0·9	4·99	0·158		2·0	5·84	0·293
	1·0	6·66	0·205		1·0	5·55	0·195				
	1·5	9·99	0·430		1·5	8·33	0·372				
	2·0	13·33	0·650		2·0	11·11	0·571				

The graphs constructed from these results give nearly parallel lines beyond a concentration of *ca.* 0·2 × 10^{-6} g.-mol/25 c.c., with the glucose curve lying equidistant from the xylose and maltose curves. By analogy it is assumed that the hypothetical disaccharide related to xylan, as is maltose to starch, would give an absorption curve as far removed from that of xylose as is maltose from glucose, and this in fact would correspond with the experimental curve for glucose. For estimating the proportion of reducing groups in xylan, two equal samples (50—75 mg.) of xylan were dissolved in sodium hydroxide (1 c.c.; 6N.), and the same volume of 3 : 5-dinitrosalicylic acid was added to one of them, the nitrosalicylic acid for the blank being measured into a 25-c.c. standard flask. The volumes of both samples were made up to 7 c.c. with water and both samples were heated at 65° for 30 minutes. The solutions were cooled and made up to 25 c.c., and blank and unknown compared as before: 73·35 mg. of xylan gave log $I/I_0 = 0{\cdot}30$, corresponding to 60 $C_5H_8O_4$ units (xylose curve) or 72 units (glucose curve); 58·15 mg. of xylan gave log $I/I_0 = 0{\cdot}172$, *i.e.*, 63 (xylose curve) or 79 units (glucose curve).

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KING'S BUILDINGS, THE UNIVERSITY OF EDINBURGH.
THE UNIVERSITY OF BRISTOL.

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263. *Studies on Fructosans. Part I. Inulin from Dahlia Tubers.*

By E. L. HIRST, D. I. MCGILVRAY, and E. G. V. PERCIVAL.

Repeated purification of inulin isolated from the tubers of a known variety of Dahlia failed to remove combined glucose (*ca.* 6%).

Methylated inulin on hydrolysis and separation by solvent extraction and by chromatography on a cellulose column gave 3 : 4 : 6-trimethyl fructose (91%) and tetramethyl fructofuranose (3·2%), together with tetramethyl glucopyranose (2·2%) and a mixture of trimethyl glucoses (3·7%). No dimethyl hexoses were detected, so that a branched structure is excluded. The principal trimethyl glucose component appears to be the 2 : 4 : 6-isomer. The high proportion of tetra- to tri-methyl glucose suggests that the glucose does not arise from the hydrolysis of an associated polyglucosan but is attached directly to the fructofuranose chain. Possible structures are suggested with a chain of about 35 fructofuranose residues with the potentially reducing fructose residue linked to a glucopyranose unit by a sucrose-type linkage, with a second glucopyranose residue linked through $C_{(1)}$ and $C_{(3)}$ at some undetermined position in the chain. The alternative possibility of a trehalose-type linkage between the two glucose residues is considered to be unlikely.

IN previous work on the constitution of inulin (Haworth, Hirst, and Percival, *J.*, 1932, 2384), it was deduced that the polysaccharide, which had been shown previously (Haworth and Learner, *J.*, 1928, 619) to be composed mainly of D-fructofuranose residues linked through the 1 : 2-positions was made up of a chain of *ca.* 30 such units. This conclusion was reached on the basis of the isolation of tetramethyl fructofuranose (3·7%) on the hydrolysis of methylated

inulin. No methylated glucose derivatives were recognised among the products of hydrolysis, but Irvine and Montgomery (*J. Amer. Chem. Soc.*, **1933**, **55**, 1988) claimed that 3 : 4 : 6-trimethyl glucose, in small and variable amounts, accompanied the 3 : 4 : 6-trimethyl fructose and tetramethyl fructofuranose of methylated inulin hydrolysates, and it was claimed that the first sugar was produced from the second in some way by the agency of the acid hydrolytic agent.

Many workers, however (Tanret, *Bull. Soc. chim.*, **1893**, [iii], **9**, 233; Schlubach and Elsner, *Ber.*, **1929**, **62**, 1493; Adams, Richtmyer, and Hudson, *J. Amer. Chem. Soc.*, **1943**, **65**, 1369; Ohlmeyer and Pringsheim, *Ber.*, **1933**, **66**, 1292), have reported the presence of glucose in the products of hydrolysis of inulin, but it has always been uncertain whether the aldose originated in an associated polyglucosan, was produced from fructose, or formed an essential part of the inulin molecule. With the improved methods of analysis now available it was hoped to throw light on this subject.

Seven recrystallisations from water of a specimen of inulin ($[\alpha]_D$ $-40°$) isolated from "Blue Danube" dahlia tubers failed to remove glucose from the polysaccharide, the quantity amounting to 5·7% estimated by paper-strip chromatography (Flood, Hirst, and Jones, *J.*, **1948**, 1697) and corresponding to one glucose residue in *ca.* 19 hexose units.

The dahlia inulin was methylated in an atmosphere of nitrogen with sodium hydroxide and methyl sulphate, followed by a treatment with methyl iodide and silver oxide. The methylated inulin was then hydrolysed by oxalic acid in methanolic-aqueous solution, and the products were converted into glycosides with methanolic hydrogen chloride. The mixture was then extracted in a liquid-extractor with light petroleum, as described by Brown and Jones (*J.*, **1947**, 1344), to give a mixture of methylglycosides (A), and thereafter with chloroform to give another mixture (B).

Examination, by the paper chromatogram, of the sugars obtained on the hydrolysis of A and B indicated, apparently, the presence of two components of R_G 0·88 and R_G 1·00, respectively. Tetramethyl fructofuranose and tetramethyl glucopyranose have the same R_G value (1·00), but it was possible to distinguish between these sugars and to identify them on the chromatogram when both were present, by the use of aniline oxalate to detect the glucose derivatives, and of urea oxalate (private communication by Dr. J. K. N. Jones) for the methylated fructoses. In this way A was found to contain most of the tetramethyl methylfructofuranoside, together with trimethyl fructose and trimethyl glucoses, whilst B contained tetramethyl methylglucopyranoside with only a little tetramethyl methylfructofuranoside, together with trimethyl sugars as before. A further separation was then carried out on a column of powdered cellulose (Hough, Jones, and Wadman, *J.*, **1949**, 2511) after conversion of the glucosides into the free sugars. Pure tetramethyl fructofuranose was isolated from A together with a mixture of trimethyl fructose and trimethyl glucoses. B gave a much smaller yield of tetramethyl fructofuranose, mixed with crystalline tetramethyl glucopyranose, the relative proportions being determined by hypoiodite oxidation; the same method was adopted for the evaluation of the mixtures of trimethyl sugars arising from both A and B.

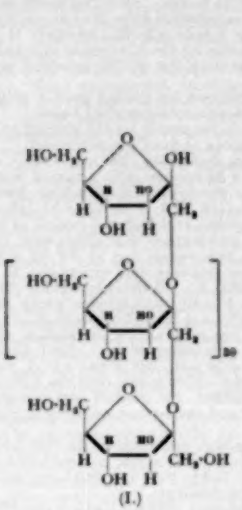
From these experiments it was computed that methylated dahlia inulin gave, on hydrolysis, tetramethyl fructofuranose 3·2%, tetramethyl glucopyranose 2·2%, 3 : 4 : 6-trimethyl fructofuranose 90·9%, and trimethyl glucoses 3·2%. It will be observed that the quantity of methylated glucoses estimated is in good agreement with the glucose content of the polysaccharide.

Owing to the identity of the R_G values of the trimethyl fructofuranose and the trimethyl glucoses, at any rate in the solvent mixtures employed, we were compelled to abandon direct chromatographic methods of separation and to seek others. Partial success was achieved by oxidation with bromine to give the corresponding aldonic acids, followed by the removal of the excess of trimethyl fructofuranose on the cellulose column. The trimethyl glucoses were eventually isolated as methyl esters, the derived amides from which gave a negative Weerman reaction and yielded no formaldehyde on oxidation with periodate. It was diagnosed, therefore, that methoxyl groups were present on $C_{(2)}$ and $C_{(4)}$. To decide between the possible alternatives, 2 : 4 : 6- and 2 : 3 : 6-trimethyl gluconamides, the possibility of the presence of glucofuranose units in the polysaccharide being neglected, the total consumption of periodate was measured in comparison with that of 2 : 3 : 6-trimethyl gluconamide. The result indicated that 71% of the unknown was not attacked by periodate. It is possible, therefore, that the principal component of the mixture was 2 : 4 : 6-trimethyl gluconamide, but we are well aware of the danger of relying exclusively on evidence in which the isolation of crystalline derivatives plays no part.

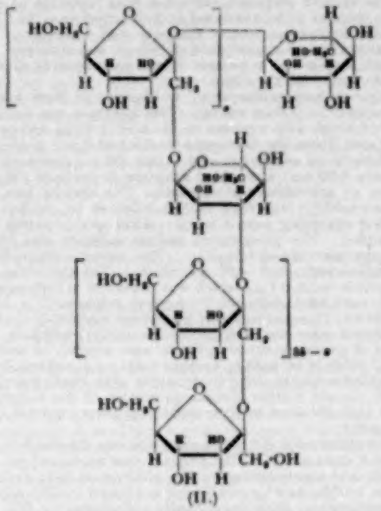
It is noteworthy that no dimethyl hexoses were encountered in this investigation, so that

the isolation of tetramethyl glucopyranose cannot be accounted for by the postulation of a branched structure. Furthermore, it appears most unlikely that the glucose is derived from an associated polysaccharide, for the high ratio of tetra- to tri-methyl glucose is inexplicable on this basis.

We appear to be left, therefore, with two main alternatives, both of which concern the potential reducing group of the main chain of fructofuranose units, the basic features of which were outlined by Haworth and Learner, and by Haworth, Hirst, and Percival (*loc. cit.*) (I).



(I.)



(II.)

The amount of glucose found corresponds to 2 units in a total of 38 hexose units. A structure such as that depicted in (II), on methylation and hydrolysis, would give tetramethyl fructofuranose 3·0% (3·2), tetramethyl glucopyranose 3·0% (2·2), 2 : 4 : 6-trimethyl glucose 2·8% (2·6), and 3 : 4 : 6-trimethyl fructose 91·5% (90·9); the figures in parentheses represent the observed values. It is seen that the chain is terminated by the type of linkage present in sucrose, although no claim can be made to any knowledge of the stereochemical arrangements of the glycosidic linkages. So far as the present evidence goes, the glucose isolated as trimethyl glucose could occur at any intermediate point of the chain and could adjoin the terminal glucose unit. There is another formal possibility, with two glucose residues united as in the trehalose series terminating the chain, but this structure can be dismissed because of the stability of the trehalose linkage. Either formulation would give 1 mole of formic acid from 38 hexose units on oxidation with periodate, and the methylated derivative would have a molecular weight of 7800. The corresponding values found experimentally were 1 formic acid from 48 hexose units and 6210 (Carter and Record, *J.*, 1939, 624).

Although the constitution of inulin cannot be decided without further study, independent evidence exists which can be interpreted as supporting the views outlined above. Bacon and Edelman (*Biochem. J.*, 1949, **45**, xxviii) have reported that in extracts from the subterranean organs of several species of *Compositæ*, *e.g.*, Jerusalem artichoke tubers, at least six fructose-containing components are present, of which one is sucrose and the remainder have R_F values on the chromatogram ranging between that of sucrose and zero. Furthermore these authors have demonstrated that on hydrolysis under mild conditions the polysaccharide portion gives rise to both glucose and fructose. These studies by Bacon and Edelman (*loc. cit.*) and by Edelman and Bacon (*loc. cit.*, p. xxix) on the enzymic degradation of inulin are clearly highly important and may eventually throw light on the mechanism of its biosynthesis.

Experimental.

Isolation of Dahlia Inulin.—Dahlia tubers (3·3 kg.), variety "Blue Danube" purchased from Dobbie and Co., were minced (February, 1948), and the expressed juice was filtered through cloth. After an hour the filtrate solidified; it was then treated with hot water (1500 c.c.), milk of lime was added to pH 8, and the precipitate removed by filtration. Dilute aqueous oxalic acid was added to the solution at 60—70° to give pH 7, followed by decolorising charcoal; after filtration and chilling to *ca.* 3°, inulin separated. The separated solid (1*a*) was kept in acetone overnight and dried (50 g.).

The mother-liquor was concentrated at 40°/15 mm. to 300 c.c. and a further crop of inulin (1*b*; 35 g.) was isolated.

The minced pulp was extracted with water (5 l.) at 60° for 1½ hours. After treatment as above inulin (2*a*; 64 g.) was isolated and a further crop (2*b*; 108 g.) was obtained from the mother-liquor.

By a final extraction of the pulp with water (4 l.) at 60° for 1 hour a further quantity (3; 29 g.) of inulin, making a total yield of 286 g., was isolated. Examination by the filter-paper chromatogram showed glucose to be present in the hydrolysates of all five fractions, the specific rotations of which varied from −34° to −38°.

Eight "recrystallisations" of fraction 2*b* from hot water followed by chilling gave a product $[\alpha]_D^{20}$ −40·0° (*c*, 1·0 in water). This specimen was used in the experiments described below.

Hydrolysis with aqueous oxalic acid (2·25%) and estimation of the sugars by the method of Flood, Hirst, and Jones (*loc. cit.*) gave fructose 94·0 and glucose 5·7% (mean of five determinations).

Methylation of Inulin.—To inulin (20 g.) dissolved in sodium hydroxide (280 c.c.; 35%) methyl sulphate (120 c.c.) was added dropwise in portions (25 c.c.) every 30 minutes with constant stirring at 35°, in an atmosphere of nitrogen. The stirring was continued overnight. More sodium hydroxide (200 c.c.; 35%) was then added, followed by methyl sulphate (120 c.c.) in portions as before, the addition extending over 8 hours. After neutralisation with sulphuric acid half the volume of ethanol was added. The precipitated sodium sulphate was filtered off and washed with chloroform and the washings were dried (Na_2SO_4). The aqueous-ethanolic filtrate was evaporated at 35°/15 mm. and the residue extracted with chloroform. The combined chloroform extracts were evaporated to give a pale yellow solid (17 g.) which was dissolved in boiling acetone (500 c.c.). Sodium hydroxide (250 c.c.; 30%) was added, followed by methyl sulphate (3 × 25 c.c.) at 55—60° with stirring under nitrogen as before. This was followed by sodium hydroxide (150 c.c.; 30%) and methyl sulphate (2 × 25 c.c.). Five hours after the addition of the methyl sulphate, acetone was removed by distillation, and the pellets of partly methylated inulin were filtered off and washed with boiling water. After dissolution of the product in boiling acetone (400 c.c.) sodium hydroxide (150 c.c.; 30%) was added, followed by methyl sulphate (50 c.c.) dropwise with stirring under nitrogen. Five hours after the termination of this process further similar quantities of the reagents were added, the product was recovered as before and dissolved in chloroform, the solution dried (Na_2SO_4), and the solvent removed (diminished pressure).

The white solid (18 g.) so obtained was dissolved in methyl iodide, and silver oxide (100 g.) added during 5 days at 45°. The product was recovered by extraction in chloroform, concentration of the extract, and precipitation by the addition of light petroleum (b. p. 40—60°), two fractions, (*a*) 4·2 g. (Found: OMe, 44·9%) and (*b*) 7·4 g. (Found: OMe, 45·5%), being obtained.

Hydrolysis of Methylated Inulin.—Fraction (*b*) (7·0 g.) in methanol (210 c.c.) and water (70 c.c.) was heated with crystallised oxalic acid (2·8 g.) at 80° for 18 hours. The solution was then neutralised with calcium carbonate and evaporated at 40°/15 mm., the syrup extracted with chloroform, and the extract dried (Na_2SO_4), evaporated to a syrup which was dissolved in methanol containing hydrogen chloride (0·25%), and kept at 20° for 70 hours. Barium carbonate was then added, the solvent removed in the presence of the solid, and the residue extracted with chloroform which on distillation at 40°/15 mm. gave a syrup (7·57 g.) which was kept in a vacuum over phosphoric oxide.

Partial Fractionation by Solvent Extraction.—The above syrup was dissolved in water (50 c.c.) and, in the presence of a little barium carbonate, was extracted with purified light petroleum (b. p. 40°) in a liquid-extractor (Brown and Jones, *loc. cit.*) for 3 periods of 3 hours each. The solvent was removed from these extracts, and samples were examined in duplicate on the paper chromatogram after hydrolysis with oxalic acid (0·4 c.c.; 2·25%) at 80° for 2 hours, using urea oxalate as a developing agent (for fructose derivatives) and aniline oxalate. All three samples contained tetramethyl fructofuranose, trimethyl fructose, and trimethyl glucose, and a trace of tetramethyl glucopyranose was present in the third extract. The fractions were then combined to give (A) (1·76 g.).

The original aqueous solution was exhaustively extracted with chloroform, and the extracts were evaporated to give (B) (5·80 g.), a sample of which on hydrolysis and examination on the paper chromatogram was shown to contain tetramethyl glucopyranose, trimethyl fructose, and trimethyl glucose.

Fractionation on the Cellulose Column.—A column of powdered cellulose was prepared in a tube 50 × 3·5 cm., according to Hough, Jones, and Wadman (*loc. cit.*), the column being *ca.* 40 cm. long. The solvent employed for elution was a mixture of purified light petroleum (b. p. 100—120°) (70%) with *n*-butanol saturated with water (30%). Fraction A was hydrolysed with aqueous oxalic acid (120 c.c.; 4%) at 80° for 3 hours. The acid was neutralised with calcium carbonate, and the mixture heated at 90° for 30 minutes. The filtered solution was evaporated to a syrup (1·43 g.) and dried with benzene–ethanol. This syrup was dissolved in the minimum of the solvent and added by pipette to the top of the column, which was then developed with solvent (200 c.c.), no sugars passing through at this stage. The column was then clamped above the rotating disc containing the receiving tubes, which changed position each six minutes, 400 c.c. of solvent being placed in the constant-head flask. When the disc had moved through a circumference the contents of each tenth tube were evaporated and the residue, if any, analysed on the paper chromatogram. Tetramethyl sugars were found in tubes 30—55, and tubes 65 onwards contained trimethyl sugars only. The contents of the first set of tubes were evaporated to give a syrup (*a*) (199 mg.). The contents of the remaining tubes were also concen-

trated and the concentrate (*b*) was set aside. The column was then washed with water to remove the remainder of the trimethyl fraction (*c*).

Fraction B was hydrolysed, and the reducing syrup (5·28) in the minimum of solvent added to the cellulose column. The tetramethyl hexose portion of this eluate (*d*) (198 mg.) was obtained by the evaporation of tubes 15—55; the trimethyl sugars were obtained as before and combined with (*b*) and (*c*) to give (*e*) (5·685 g.) (total recovery, 90·6%).

Fraction (*a*). Examination on the paper chromatogram showed this syrup, $[\alpha]_D^{15}$ +42·1° (*c*, 1·0 in water), to be a mixture of tetramethyl fructofuranose and tetramethyl glucopyranose.

The proportion of tetramethyl glucose was estimated as follows. A known quantity (*ca.* 60 mg.) was dissolved in water (5 c.c.), the opalescence due to a trace of grease removed with "Filter Cel," and the solution filtered. Portions of this solution (*ca.* 500 mg.) were weighed accurately into tubes fitted with ground-glass stoppers, and buffer (pH 11·4; 5·0 c.c.) was added, followed by iodine solution (N/10; 2·5 c.c.). The stoppers were sealed with 10% potassium iodide solution, and the tubes kept at room temperature for 4 hours. Sulphuric acid (4N.; 2·5 c.c.) was then added and the iodine liberated was titrated with sodium thiosulphate (0·02N.). Tubes containing water were treated in an identical manner. Pure tetramethyl fructofuranose having been tested [water blank 12·390 c.c.; solution (63 mg./5 c.c.) 12·385 c.c.] and found not to react with alkaline hypoiodite, the proportion of tetramethyl glucose was estimated to be 13%; it was concluded that (*a*) contained 173 mg. of tetramethyl fructofuranose and 26 mg. of tetramethyl glucopyranose.

Fraction (*d*). Examination on the chromatogram showed the tetramethyl glucopyranose to be contaminated with trimethyl fructose. This syrup was, therefore, separated again on the column, and tetramethyl glucose (135·4 mg.) crystallised completely after evaporation and keeping overnight (*d'*). The trimethyl sugar from this separation was added to (*e*) to give a total of 5·783 g.

Fraction *d'* was not pure tetramethyl glucopyranose; it showed $[\alpha]_D^{15}$ +68° (*c*, 1·0 in water), and hypoiodite oxidation gave a value of 80·7% aldose. It is estimated, therefore, that 109·3 mg. of tetramethyl glucopyranose and 26·1 mg. of tetramethyl fructofuranose were present.

Fraction *d'* was converted into tetramethyl glucopyranose anilide, m. p. 134—135° unchanged on admixture with an authentic specimen (Found: C, 61·7; H, 7·0; N, 4·6; OMe, 38·2. Calc. for $C_{16}H_{25}O_5N$: C, 61·6; H, 8·0; N, 4·5; OMe, 39·8%).

Fraction (*e*). Examination on the paper chromatogram showed (*e*) to contain trimethyl glucose and a trimethyl fructose of identical R_G value, $[\alpha]_D^{15}$ +38° (*c*, 0·9 in water) (Found: OMe, 38%). Hypoiodite oxidation gave an aldose equivalent of 3·9%, which corresponds to 225 mg. of trimethyl glucose and 5·558 mg. of trimethyl fructose.

To sum up, the total sugars estimated amount to tetramethyl fructofuranose 0·199 (3·2%), tetramethyl glucopyranose 0·135 (2·2%), trimethyl fructofuranose 5·558 (90·9%), and trimethyl glucose 0·225 g. (3·7%).

Oxidation of fraction (*e*). Fraction (*e*) in water (60 c.c.) was treated with bromine (2 c.c.). After 4 days at 15° examination on the paper chromatogram showed that trimethyl glucose was still present, and this was still the case after the addition of more bromine and storage for a further 4 days. Lead carbonate was then added to the aqueous solution, together with bromine (2·5 c.c.), and the oxidation was continued for a further 4 days; free bromine was removed by aeration, and the solution neutralised with silver carbonate. After filtration, treatment with hydrogen sulphide was followed by concentration to a thin syrup, which was dissolved in water, neutralised by silver carbonate, and again treated with hydrogen sulphide. Examination on the paper chromatogram showed no trimethyl glucose on spraying with aniline oxalate. When a paper was run in an acidic solvent [acetic acid (10%)–*n*-butanol (40%)–water (50%)] and the dried paper sprayed with bromophenol-blue (0·05%), two yellow spots were observed 4·5 cm. and 5·8 cm. respectively above the solvent boundary.

The syrup was then transferred to a cellulose column and the column eluted with the butanol–light petroleum solvent (1 l.) used previously. The upper 15 cm. of packing were then removed and extracted with water. After evaporation at 40°/15 mm. the residue was esterified with methanolic hydrogen chloride (15 c.c.; 2%) for 9 hours at 65°, the solution neutralised with silver carbonate, and silver in solution removed as sulphide. On removal of the methanol a brown syrup remained which was transferred to a distillation flask. Distillation gave fractions (*w*) bath temperature 90—120°/0·01 mm. (40 mg.) (Found: OMe, 53·0%), and (*x*) bath temperature 120—200°/0·01 mm. (170 mg.). Fraction (*x*) was contaminated with sulphur which was removed by extraction with hot water, filtration, and evaporation, to give (*y*) (50 mg.) (Found: OMe, 45·0%).

Amide formation. Fraction (*w*) was dissolved in methanolic ammonia (3 c.c.) and kept at 0° for 4 days. Crystals of (−)-D-dimethoxysuccinamide separated, having m. p. 283°, $[\alpha]_D^{15}$ −90° (*c*, 1·2 in water) (Found: C, 40·7; H, 6·7; OMe, 34·0. Calc. for $C_6H_{12}O_4N_2$: C, 40·9; H, 6·8; OMe, 35·2%). It was concluded that (−)-D-dimethoxysuccinic acid had been produced from 3 : 4 : 6-trimethyl D-fructose by degradative oxidation, owing to the prolonged contact with bromine.

The syrupy residue obtained on evaporating the methanolic solution was added to the syrupy amide from (*y*).

Fraction (*y*) was treated as above with methanolic ammonia, and a further small quantity of the crystalline dimethoxysuccinamide was removed. The accompanying syrup (49 mg.) had OMe, 35·0% (Calc. for $C_7H_{14}O_4N$: OMe, 36·7%). The syrupy amide (7·4 mg.) in water (2 c.c.) was treated with N-sodium hydrogen carbonate (2 c.c.), followed by periodic acid (2 c.c.; 0·3M.). After 1 hour at 15° hydrochloric acid (3 c.c.; N.) and sodium arsenite (2 c.c.; N.) were added. When the precipitate and yellow colour had disappeared sodium acetate (2 c.c.; N.) and dimedon reagent (1 c.c. containing 85 mg./c.c. in 95% ethanol) were added. A control experiment with gluconamide (9·2 mg.) was carried out. This gave 8·4 mg. of the formaldehyde–dimedon complex (70% of theory), but the amide under investigation gave no formaldehyde.

The amide (12·0 mg.) was tested by the Weerman reaction, with gluconamide as a control: no hydrazodicarbonamide was obtained. To the amide (18·0 mg.) in water (1·5 c.c.) was added sodium periodate (2 c.c.; M/4), and the mixture kept for 5 hours at 15°. A control with 2 : 3 : 6-trimethyl gluconamide

(15·2 mg.) and a water blank were similarly treated. At the end of the experiment the excess of periodate was determined by titration with sodium arsenite solution. The control used 0·95 mole of sodium periodate per $C_9H_{17}O_4N$ and the unknown syrup 0·274 mole.

Oxidation of Inulin by Periodate.—Inulin (*ca.* 50 mg.) was treated with sodium metaperiodate (10 c.c.; $\pi/8$) for varying periods, titration with sodium arsenite solution in the presence of potassium iodide being used to determine the amount of periodate remaining. Found: 18 hours, 0·665; 47 hours, 0·874; 85 hours, 0·925; 130 hours, 1·03 moles/$C_6H_{10}O_5$ (final value).

The method of Hainall, Hirst, and Jones (*J.*, 1947, 1427) was used to determine the formic acid liberated by oxidation with potassium periodate; samples of 200—300 mg., potassium chloride (1 g.), and sodium metaperiodate (10 c.c.; $\pi/4$) diluted to 50 c.c. were used, with shaking at room temperature in the dark. Samples (5 c.c.) were withdrawn at intervals and titrated with sodium hydroxide ($\pi/100$) to methyl-red after destruction of periodate with ethylene glycol. The following figures represent the number of $C_6H_{10}O_5$ residues per mole of formic acid: 138 hours, 62; 192 hours, 57; 213 hours, 49; 305 hours, 47·9; 336 hours, 47·6.

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264. *α-Methylenic Reactivity in Olefinic Systems. Part IV. The Structure of the Dimeride formed by the Stannic Chloride-catalysed Polymerisation of Trimethylethylene. Synthesis and Characterisation of Isomeric Methyl Hexyl Ketones.*

By JOHN W. BAKER.

The "methyl hexyl ketone" obtained by ozonolysis of the stannic chloride-induced dimerisation of trimethylethylene (Baker, Part II, *J.*, 1945, 724) has been separated into two isomeric ketones, (1) giving a semicarbazone, m. p. 173°, and (2) giving a semicarbazone, m. p. 154°. The identity of the former with 4 : 4-dimethyl-α-hexan-2-one has been established, thus confirming the presence of a dimeride of structure $CHMe{:}CMe{\cdot}CH_2{\cdot}CMe_2{\cdot}CH_2Me$ (*I*) derived by an addition $SnCl_4$—$\overset{\frown}{CHMe}$—$\overset{\frown}{CMe}$=$\overset{\frown}{CH_2}$ Me_2C=$\overset{\frown}{CHMe}$ $\overset{\curvearrowright}{H}$ which parallels, in the olefin system H—$\overset{\curvearrowright}{C}$—$\overset{\curvearrowright}{C}$=$\overset{\curvearrowright}{C}$, the Michael type of addition of the system H—$\overset{\curvearrowright}{C}$—$\overset{\curvearrowright}{C}$=O, to a C=C centre.

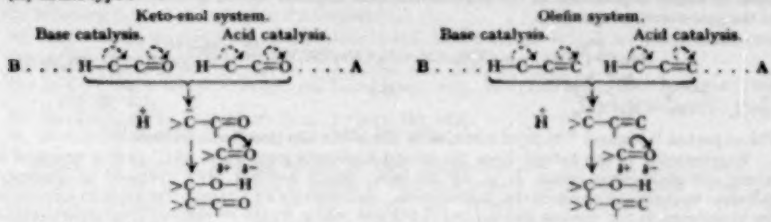
Of the remaining 16 isomeric methyl hexyl ketones, 9 have been synthesised and characterised and a further 5 are described in the literature, and none of these is identical with the second ozonolysis ketone (semicarbazone, m. p. 154°) which must therefore possess the structure $Me{\cdot}CO{\cdot}CHMeBu^t$ or $Me{\cdot}CO{\cdot}CH_2{\cdot}CH_2Bu^t$. Attempts to synthesise both these ketones have proved unsuccessful. Either structure would necessitate considerable skeletal change in the trimethylethylene during dimerisation, and the implications of these results on the dimerisation of tetramethylethylene (Brunner and Farmer, *J.*, 1937, 1039) are briefly discussed.

THE object of this series of investigations is to ascertain to what extent an olefinic system H—$\overset{\frown}{CH_2}$—$\overset{\frown}{CR}$=$\overset{\curvearrowright}{CR_2}$, activated by hyperconjugation, can undergo reactions of the types exhibited by the system H—$\overset{\frown}{CH_2}$—$\overset{\curvearrowright}{CR}$=O (cf. Part I, *J.*, 1944, 296).

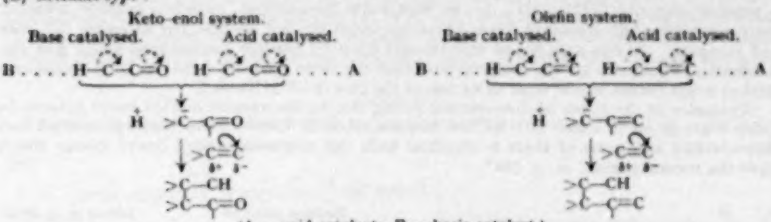
An essential feature of the latter system is its capacity to add, as the ionic fragments $\overset{+}{H}$ $\overset{-}{CH_2}$—CR=O, to carbonyl, C=O, and olefinic, C=C, centres in the well-known aldol and Michael reactions. If the olefinic system can behave as the weak conjugate acid of the strong carbanion base $\overset{-}{CH_2}$—CR=CR_2 analogy suggests that it might undergo additive reactions of essentially the same types. The comparison is summarised in the scheme on p. 1303.

The catalyst has a dual function: (i) to assist the removal of the (ionising) proton and (ii) to increase the polarisation of the unsaturated centre so as to activate it towards nucleophilic attack (cf. Baker and Rothstein, "Handbuch der Katalyse," Vol. II, Vienna, 1940, p. 168). In the keto–enol system basic catalysis is the more effective, first because it operates by direct attack on the ionising hydrogen and secondly because the resulting carbanion already contains, in its carbonyl oxygen atom, a suitable seat for the anionic charge $\overset{\curvearrowright}{C}$—C=O ↔ C=C—$\overset{\curvearrowleft}{O}$

(A) *Aldol type* :

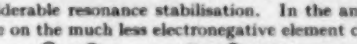


(B) *Michael type* :

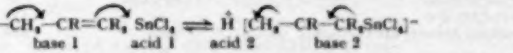


(A = acid catalyst ; B = basic catalyst.)

this ion thus possessing considerable resonance stabilisation. In the analogous olefin system the anionic charge must reside on the much less electronegative element carbon,



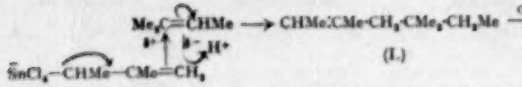
unless the catalyst can accept the electron pair and so provide a more stable seat for it. It would therefore be expected that the most effective type of catalyst for parallel olefin additive reactions would be non-hydrogen *acids*, such as stannic chloride, boron trifluoride, etc., functioning in the manner already indicated in Part II (*J.*, 1945, 725), *viz.* :



Olefin additions of type (A), *i.e.*, to C=O, have already been described in Parts I and II (*locc. cit.*). This communication deals with an addition of type (B) to C=C, *viz.*, the self-addition or dimerisation of trimethylethylene.* As indicated in Part II (*loc. cit.*, p. 727) fractionation of the polymerisation products isolated as by-products during the study of the stannic-chloride-catalysed reaction of trimethylethylene with phenyl *iso*cyanate gave three main fractions, the one of lowest b. p. (~55°/15 mm.) consisting essentially of a dimeride $C_{10}H_{20}$. Repeated fractionation of this led to the isolation of a fraction of constant b. p. 46°/12 mm. This on ozonolysis gave, as the volatile product, only acetaldehyde, identified as its *p*-nitrophenylhydrazone, 2 : 4-dinitrophenylhydrazone, and dimedon compound, indicating a =CHMe end group. No trace of formaldehyde or other carbonyl compound derived from any different end group could be detected in any experiment, including one in which the dimeride fraction employed was prepared by direct stannic chloride polymerisation of a different, carefully fractionated specimen of trimethylethylene in the absence of any complicating phenyl *iso*cyanate. This dimeride gave products identical with those obtained from the dimeride isolated as a by-product in the phenyl *iso*cyanate experiments. The other fraction of the molecule was a mixture of two isomeric methyl hexyl ketones, which were separated by fractional crystallisation of the semicarbazones into two pure semicarbazones, m. p. 173° and 154°, both of which have the composition $C_9H_{19}ON_3$. The former has now been proved by direct comparison to be the semicarbazone of 4 : 4-dimethyl-*n*-hexan-2-one (II) and thus the ambiguity reported in the preliminary investigation (Part II, p. 727) has been removed. The proved structure of this ketone means that the structure of one of the dimerides must be (I), derived by a type B addition of one molecule of trimethylethylene to a second molecule, the double

* A short summary of some of these results was published earlier (*Nature*, 1948, **161**, 171).

bond of which is polarised in the normal direction imposed by the greater electron-repulsion of the *gem*-dimethyl grouping :



(I.)

The expected " Michael " type of addition in the olefin has thus been realised.

Regeneration of the ketone from the second semicarbazone, m. p. 154°, gave a liquid of a strong camphoraceous odour, b. p. 66°/60 mm., which has not been obtained in quantity sufficient to carry out a systematic degradation. Accordingly an attempt was made to formulate the structures of the various methyl hexyl ketones which would be derived from dimerisation of trimethylethylene, its prototropic isomers, $CH_2{:}CMe{\cdot}CH_2Me$ and $CH_2{:}CH{\cdot}CHMe_2$, and even a possible impurity $CHMe{:}CHEt$, by all reasonable mechanisms, including possible pinacolic rearrangements, but excluding those dimerides which did not contain the necessary $=CHMe$ end grouping. It was soon found that several different possible mechanisms would give rise to identical structures for the dimeride and that the more probable structure of the unknown methyl hexyl ketone would seem to be one of the Nos. 1—7 of Table I.

Examples of the types of dimerisation giving rise to the various methyl hexyl ketones in Table I are given in Table II. All the ketones listed in Table I have been synthesised and characterised and none of them is identical with the unknown methyl hexyl ketone which gives the semicarbazone, m. p. 154°.

TABLE I.

No.	$Me{\cdot}CO{\cdot}C_6H_{11}$.	Melting point of 2 : 4-dinitrophenylhydrazone.	Melting point of semicarbazone.	Mixed m. p. with semicarbazone, m. p. 154°.
1.	$Me{\cdot}CO{\cdot}CH_2{\cdot}CHMePr^i$	71°	162°	147—150°
2.	$Me{\cdot}CO{\cdot}CMe_2Pr^i$	—	153	139—140
3.	$Me{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2Pr^i$	76	153—155	126—140
4.	$Me{\cdot}CO{\cdot}CHMe{\cdot}CHMeEt$	—	141	124—138
5.	$Me{\cdot}CO{\cdot}CHMe{\cdot}CH_2Pr^i$	55	115	103—108 (indefinite)
6.	$Me{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CHMeEt$	67	138·5	110 (indefinite)
7.	$Me{\cdot}CO{\cdot}CH_2{\cdot}CHMePr^n$	54	108	101
8.	$Me{\cdot}CO{\cdot}CHEtPr^n$	62—64	81	70—80
9.	$Me{\cdot}CO{\cdot}CHEtPr^i$	—	121·5	105—120
	Ozonolysis ketone, $Me{\cdot}CO{\cdot}C_6H_{12}$	82	154	—

References :

(2) Locquin and Leers, *Compt. rend.*, 1924, **179**, 55; *Bull. Soc. chim.*, 1926, [iv], **39**, 436.
(3) Heilbron and Thompson, *J.*, 1929, 888; Locquin and Heilmann, *Bull. Soc. chim.*, 1929, [iv], **45**, 875; Wieland, *Ber.*, 1925, **58**, 2015.
(4) Powell and Secoy, *J. Amer. Chem. Soc.*, 1931, **53**, 768.
(7) Clarke, *Amer. Chem. J.*, 1908, **30**, 93; *Ber.*, 1907, **40**, 353.
(8) Clarke and Riegel, *J. Amer. Chem. Soc.*, 1912, **34**, 679.
(9) Clarke, *ibid.*, 1908, **39**, 577.

The ketones in Table I were synthesised in accordance with the following schemes :

(1) $Me{\cdot}CO{\cdot}CH_2{\cdot}COMe + 2MgPr^iBr \longrightarrow Me{\cdot}C(O{\cdot}MgBr){:}CH{\cdot}C(OH)MePr^i \longrightarrow Me{\cdot}CO{\cdot}CH_2{\cdot}C(OH)MePr^i \longrightarrow Me{\cdot}CO{\cdot}CH{:}CMePr^i$ (or isomer) $\xrightarrow{Pt\text{-}H_2}$ (I).

(2) $CMe_2{:}CH{\cdot}COMe + Br_2 \longrightarrow CMe_2Br{\cdot}CHBr{\cdot}COMe \xrightarrow{\text{piperidine}} CMe_2{:}CBr{\cdot}COMe \xrightarrow{NaOAc} CMe_2{:}C(OAc){\cdot}COMe \xrightarrow{10\%\ H_2SO_4} CHMe_2{\cdot}CO{\cdot}COMe$ (Dufraisse and Moureu, *Bull. Soc. chim.*, 1927, [iv], **41**, 855; Pauly and Leick, *Ber.*, 1900, **33**, 503) $\xrightarrow{2MgMeI} CMePr^i(OH){\cdot}CMe_2(OH) \xrightarrow{Conc.\ H_2SO_4} Me{\cdot}CO{\cdot}CMe_2Pr^i$ (Locquin and Leers, *loc. cit.*).

The remaining ketones were synthesised by the usual acetoacetic ester syntheses from the appropriate alkyl bromide–acetoacetic ester pair, concentrated hydrochloric acid being used for hydrolysis of the alkylacetoacetic ester. As the m. p. and the mixed m. p. of their semicarbazones show, none of these ketones is identical with the second ozonolysis ketone. Of the seventeen theoretically possible isomerides of methyl hexyl ketone, nine were thus synthesised whilst a tenth is **4** : 4-dimethyl-*n*-hexan-2-one (II), already proved to be identical

with the other ozonolysis ketone giving a semicarbazone, m. p. 173°. Of the remaining seven the following five are described in the literature :

10. Me·CO·[CH_2]$_4$·Me (123°) (Michael, *J. Amer. Chem. Soc.*, 1919, **41**, 417; Bouveault and Locquin, *Bull. Soc. chim.*, 1904, [iv], **31**, 1167).
11. Me·CO·CHMeBu^n (82°) (Powell, *J. Amer. Chem. Soc.*, 1924, **46**, 2516).
12. Me·CO·CMe$_2$Pr^n (119·5°) (Locquin and Leers, *Compt. rend.*, 1924, **178**, 2097; *Bull. Soc. chim.*, 1926, [iv], **39**, 433).
13. Me·CO·CH_2·CHEt$_2$ (141—142°) (Kon, *J.*, 1921, **119**, 822).
14. Me·CO·CMeEt$_2$ (168°) (Nybergh, *Ber.*, 1922, **55**, 1962).

Unless the recorded melting points of their semicarbazones (given in parentheses) are seriously in error, none of these is identical with the second ozonolysis ketone. The only remaining possible structures of the latter are therefore Me·CO·CHMeBu^t (15) or Me·CO·CH_2·CH_2·Bu^t (16). Unfortunately both these are difficult to synthesise since the most obvious method, the acetoacetic ester synthesis, involved the alkylation of ethyl methylacetoacetate with a *tert.*-butyl halide (for 15) or of ethyl acetoacetate with a *neo*pentyl halide (for 16), both of which, as the work of Hughes, Ingold, and their collaborators has demonstrated, would be subject to very strong steric hindrance. Nor could this difficulty be evaded

TABLE II.

Examples of mechanism of dimerisation to give ketones of structures in Table I (A = $SnCl_4$).

No.

1. $\bar{A}$—CHMe—CMe=CH_2 CHMe=CMe_2 $\overset{+}{H}$
   or
   CH_2—CH=CMe_2 ⇌ CH_2=CH—$CHMe_2$
   $\overset{+}{H}$ CH_2=CMe—CHMe—$\bar{A}$
   → CHMe·CMe·CH_2·CHMe·$CHMe_2$ $\xrightarrow{O_3}$ (1)

2. CMe_2=CHMe $\overset{+}{C}Me_2$—CHMe—$\bar{A}$ → $\overset{+}{C}Me_2$—CMe·CMe_2·CHMe—$\bar{A}$ →
   (H)
   CMe_2=CMe—CMe—CHMe—$\bar{A}$ → $CHMe_2$·CMe_2·CMe·CHMe $\xrightarrow{O_3}$ (2)
   $\overset{+}{H}$ (Corollary of Price's mechanism : cf. Baker, *Nature*, *loc. cit.*).

3. CH_2—CH=CMe_2 ⇌ $CHMe_2$—CH=CH_2 CH_2=CMe—CHMe—$\bar{A}$ →
   $\overset{+}{H}$ $CHMe_2$·[CH_2]$_2$·CMe·CHMe $\xrightarrow{O_3}$ (3)

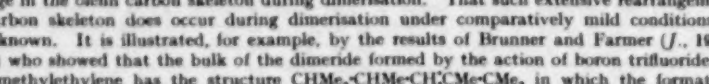
4. CMeEt=CH_2 $\overset{+}{C}Me_2$—CHMe—$\bar{A}$ → CMeEt—CH—CMe_2—CHMe—$\bar{A}$ →
   (H)
   CMeEt=CH—CMe—CHMe—$\bar{A}$ → CHMeEt·CHMe·CMe·CHMe $\xrightarrow{O_3}$ (4)
   $\overset{+}{H}$

5. CH_2—CH=CMe_2 ⇌ $\overset{+}{C}HMe_2$—CH=CH_2 $\overset{+}{C}Me_2$—CHMe—$\bar{A}$ →
   Me
   $CHMe_2$—$\overset{+}{C}$H—CH—CMe_2—CHMe—$\bar{A}$ → $CHMe_2$—CH=CH—CMe—CHMe—$\bar{A}$ →
   (H) $\overset{+}{H}$
   $CHMe_2$·CH_2·CHMe·CMe·CHMe $\xrightarrow{O_3}$ (5)

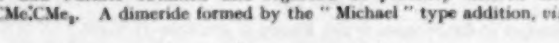
7. $\bar{A}$—CHMe—CMe=CH_2 CHMe=CHEt $\overset{+}{H}$ → CHMe·CMe·CH_2·CHMe·CH_2Et $\xrightarrow{O_3}$ (7)

by attempting the condensation under conditions favourable to a unimolecular mechanism since, for (16) this would involve rearrangement of the *neo*pentyl group to *tert.*-amyl, and the resulting ketone would then be (11). An attempt was made to effect forced condensation of *tert.*-butyl bromide with ethyl methylacetoacetate in concentrated alcoholic sodium ethoxide in a sealed tube at 120° for 7 hours, after the temperature had been slowly raised to 120° during

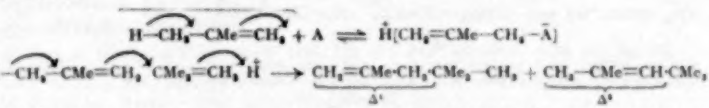
6 hours, but only volatile unsaturated products and unchanged ethyl methylacetoacetate were obtained. After a similar attempt to force the condensation of a very small quantity of *neo*pentyl bromide (kindly supplied by Professor E. D. Hughes of University College, London) with ethyl sodioacetoacetate, hydrolysis of the crude product with concentrated hydrochloric acid at 150° for 7 hours gave much tarry material and no semicarbazone could be obtained from the small amount of steam-volatile product. The structure of the second ketone must, therefore, be left indeterminate for the present. Either of the possible structures (15) or (16 would necessitate an olefin-dimeride structure which could only arise by a fairly deep-seated change in the olefin carbon skeleton during dimerisation. That such extensive rearrangement of carbon skeleton does occur during dimerisation under comparatively mild conditions is well known. It is illustrated, for example, by the results of Brunner and Farmer (*J.*, 1937, 1039) who showed that the bulk of the dimeride formed by the action of boron trifluoride on tetramethylethylene has the structure $CHMe_2{\cdot}CHMe{\cdot}CH_2{\cdot}CMe{\cdot}CMe_3$ in which the formation of a *tert.*-butyl group is again observed. Incidentally, the proof given in this paper of the structure of one dimeride of trimethylethylene which arises from a " Michael " type of olefin addition may possibly indicate the structure of the unidentified dimeride of tetramethylethylene responsible for the ozonolysis products, acetone and a methyl heptyl ketone, which Brunner and Farmer obtained and regarded as probably derived from a hydrocarbon $C_7H_{14}{\cdot}CMe{:}CMe_2$. A dimeride formed by the " Michael " type addition, *viz.* :



would yield these two products on ozonolysis. If this assumption is their unidentified methyl heptyl ketone would be 4 : 4 : 5-trimethyl-*n*-hexan-2-one. A further corollary of the proved ionisation of a proton from an olefin is the possibility of prototropic change both in the parent olefin and in the dimeride :

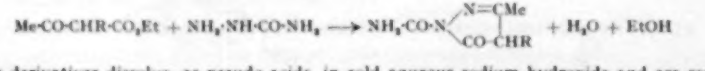


and it is not without significance that such prototropic shift superimposed on an initial addition of the " Michael " type would satisfactorily account for the structures assigned in the literature to the dimerides (formed in acid-catalysed, heterolytic polymerisation) of several simple olefins, *e.g.*, *iso*butene :



and both the Δ^1- and Δ^2-isomerides are stated to be formed (McCubbin and Adkins, *J. Amer. Chem. Soc.*, 1930, **52**, 2547). Other examples (including copolymerisations) could be quoted.

In conclusion it has been observed that certain branched-chain alkylacetoacetic esters with semicarbazide acetate do not afford their semicarbazones, but dilution of the reaction mixture after several days precipitates a deep-blue oil which slowly changes into a colourless crystalline material shown to be the corresponding carbamyl-alkylpyrazolone :



These derivatives dissolve, as pseudo-acids, in cold aqueous sodium hydroxide and are reprecipitated unchanged on careful acidification, but boiling with alkali liberates ammonia and then subsequent neutralisation of the excess of alkali with dilute acid precipitates the 3-methyl-4-alkylpyrazolone with liberation of carbon dioxide. Thiele and Strange (*Annalen*, 1894, **283**, 30) observed such pyrazolone formation when the semicarbazone of ethyl acetoacetate was kept in the presence of concentrated ammonia solution for two days at room temperature. The nature of the intermediate deep-blue oil is unknown : it may be due to traces of unrecognised metals present, since Thiele and Strange recorded that the carbamylpyrazolone gives a blue colour with ferric chloride.

Experimental.

(All microanalyses are by Drs. Weiler and Strauss, Oxford. All m. p.s are uncorrected.)

Ozonolysis of the Dimeride of Trimethylethylene.—Repeated fractional distillation either of the polymeride hydrocarbon fraction obtained as a by-product in the trimethylethylene–stannic chloride–phenyl isocyanate reaction (Part II, *loc. cit.*), or of the product of the stannic chloride-induced polymerisation of trimethylethylene alone, gave, eventually, a pure dimeride fraction, b. p. 46°/12 mm. Approx. 4-g. portions of this were dissolved either in pure chloroform or in ligroin (b. p. 40—60°) and ozonised for several days. The solvent was removed in a current of dry air at room temperature and the syrupy ozonide was decomposed by boiling with water under reflux. The volatile products escaping from the top of the condenser were passed into either (1) a solution of 2 : 4-dinitrophenylhydrazine in dilute hydrochloric acid or (2) a solution of *p*-nitrophenylhydrazine in acetic acid. Recrystallisation of the precipitated derivatives from aqueous alcohol gave acetaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 167°, and *p*-nitrophenylhydrazone, m. p. and mixed m. p. 127°. The residual aqueous liquor from the decomposition of the ozonide was extracted with ether, and the ethereal solution was shaken with aqueous sodium carbonate, washed, and dried (Na_2SO_4). Fractional distillation of the residue gave a main ketonic fraction, b. p. 37°/10 mm., together with intermediate (ketonic) fractions, b. p. 38—40°/10 mm. and 42—62°/10 mm., and a small final fraction, b. p. 83—86°/7 mm. (Found : C, 68·9; H, 11·3. $C_5H_{10}O_5$ requires C, 68·4; H, 11·4%), of an unidentified *substance* which gives only a slight turbidity with 2 : 4-dinitrophenylhydrazine and is not a peroxide. The neutralised aqueous residue from the ether-extraction was distilled and the distillate treated with dimedon. It gave only the acetaldehyde–dimedon compound, m. p. and mixed m. p. 141° after crystallisation from alcohol. The sodium carbonate extract, on acidification and ether-extraction, gave only a small amount of liquid with a strong odour of acetic acid. No trace of formaldehyde could be detected in the products of ozonolysis.

Separation of the Semicarbazones of the Ozonolysis Ketones.—The whole ketone fraction was treated with semicarbazide hydrochloride in saturated sodium acetate solution. One crop, S_1, of semicarbazone separated during the first few hours. After its removal, dilution of the reaction mother-liquor gave a second crop S_2. Treatment of S_1 with cold ether and repeated crystallisation of the insoluble portion from 96% alcohol gave the semicarbazone, m. p. 173°, of 4 : 4-dimethyl-n-hexane-2-one (II) undepressed by admixture with the semicarbazone of a synthetic specimen of this ketone obtained as described in Part II (*loc. cit.*, p. 731). The 2 : 4-*dinitrophenylhydrazone* had m. p. 78° after crystallisation from 96% alcohol (Found : C, 54·4; H, 6·6; N, 18·0. $C_{18}H_{28}O_4N_4$ requires C, 54·5; H, 6·5; N, 18·2%).

Similar fractional crystallisation of the semicarbazone fraction S_2 from ether gave the *semicarbazone*, m. p. 154°, of an unidentified methyl hexyl ketone (Found : C, 58·2; H, 10·1; N, 22·4. $C_9H_{19}ON_3$ requires C, 58·4; H, 10·3; N, 22·7%). Steam-distillation of this semicarbazone with oxalic acid, saturation of the distillate with salt, and ether-extraction gave the ketone, b. p. 66°/60 mm., which possesses a strong camphoraceous odour and gives a 2 : 4-dinitrophenylhydrazone, m. p. 82° after crystallisation from a very concentrated solution in ether–ligroin (b. p. 40—60°). The ketone gives iodoform with sodium hypochlorite and potassium iodide, but was not obtained in quantity sufficient for a systematic degradation.

Incomplete ozonolysis of the dimeride, b. p. 48—49°/17 mm., from the stannic chloride-catalysed polymerisation of a different sample of trimethylethylene alone gave acetaldehyde and a ketone, the semicarbazone of which gave the material, m. p. 173°, as the only pure product which could be isolated on fractional crystallisation. Re-ozonolysis of the recovered dimeride gave acetaldehyde and the semicarbazone, m. p. 154°, almost uncontaminated with its isomeride. Thus the dimeride of structure (I) would seem to undergo ozonolysis more rapidly than does its isomeride.

Synthesis of Isomeric Methyl Hexyl Ketones.—4 : 5-*Dimethyl*-n-*hexan*-2-*one* (1). The Grignard compound obtained from magnesium (14·4 g.) and isopropyl bromide (74 g.) in dry ether (100 c.c.) was refluxed for 30 minutes, and cooled in a freezing mixture (ice–salt). Acetylacetone (28 g., 0·5 mol. proportion) in ether (100 c.c.) was added slowly with mechanical stirring. Towards the end of the addition, separation of a sticky brown mass made stirring difficult. The reaction mixture was refluxed for 15 minutes to help to break up this mass, cooled in a freezing mixture, and decomposed with ice and ammonium chloride. The aqueous liquor was saturated with salt and repeatedly extracted with ether. Fractionation of the residue after removal of the ether (through a Widmer column) from the dried (Na_2SO_4) extract gave two main fractions : (*a*) b. p. 56—60°/11 mm. and (*b*) b. p. 120—125°/12 mm. Analysis of a redistilled specimen, b. p. 60°/11 mm., of (*a*) showed it to be essentially 4 : 5-*dimethyl*-n-*hex*-3-*en*-2-*one* (or its isomeride $CH_2{:}CPr^{i}{\cdot}CH_2{\cdot}CO{\cdot}CH_3$) (Found : C, 77·1; H, 10·7. $C_8H_{14}O$ requires C, 76·2; H, 11·1%), which affords a *semicarbazone*, m. p. 153° (sinters at 148°) after crystallisation from ether (Found : C, 58·65; H, 9·1. $C_9H_{17}ON_3$ requires C, 59·0; H, 9·3%), and a 2 : 4-*dinitrophenylhydrazone* (red), m. p. 164° after crystallisation from ether containing a trace of ethyl alcohol (Found : C, 54·35; H, 5·8. $C_{14}H_{18}O_4N_4$ requires C, 54·8; H, 5·9%). A (probably) isomeric 2 : 4-*dinitrophenylhydrazone* (orange), m. p. 120° after crystallisation from ligroin (b. p. 40—60°) (Found : C, 55·6; H, 5·6%), was obtained by dilution of the mother-liquor. The unsaturated ketone, b. p. 56—60°/11 mm., was reduced in alcohol with hydrogen and a moderately inactive platinum-black catalyst until saturated, the alcohol from the filtered solution was distilled off through a column, and the residue converted directly into its semicarbazone. Crystallisation from ether gave the 4 : 5-*dimethyl*-n-*hexan*-2-*one semicarbazone*, m. p. 162°, which depressed the m. p. of the semicarbazone of the unsaturated ketone (to 147—150°) and that (m. p. 153°) of the ozonolysis ketone (to 142—146°) (Found : C, 58·6; H, 10·2. $C_9H_{19}ON_3$ requires C, 58·4; H, 10·3%). The corresponding 2 : 4-*dinitrophenylhydrazone* had m. p. 71° after crystallisation from alcohol (Found : C, 53·7; H, 6·3. $C_{14}H_{20}O_4N_4$ requires C, 54·5; H, 6·5%). The red viscous fraction (*b*) is probably the diol, $CH_2(CMePr^{i}{\cdot}OH)_2$, and was not further examined. If only one molecular proportion of the Grignard reagent is used it merely forms the enolate of the acetylacetone which is recovered unchanged on working up the product.

3 : 3 : 4-*Trimethyl*-n-*pentan*-2-*one* (2). This was prepared essentially by a pinacolic change on

1 : 2 : 3-trimethyl-n-pentane-2 : 3-diol (Locquin and Leers, *loc. cit.*) but this diol was obtained by a different route. By use of the combined techniques of Dufraisse and Moureu (*Bull. Soc. chim.*, 1927, [iv], **41**, 855) and Pauly and Leick (*Ber.*, 1909, **42**, 503), mesityl oxide was converted successively into monobromo-, b. p. 70—71°/20 mm. (bromine in ether, followed by the action of piperidine), and acetoxy-, b. p. 74°/12 mm., mesityl oxide (by potassium acetate in absolute alcohol) which was refluxed with 10% sulphuric acid for 2—3 hours to give 4-methyl-n-pentane-3 : 4-dione (methyl*iso*propylglyoxal), b. p. 115—116°, as a very volatile, bright yellow liquid, characterised as its *disemicarbazone*, m. p. 223° (decomp.) after crystallisation from boiling alcohol (in which it is not very soluble) (Found: C, 42·3; H, 7·1. $C_9H_{16}O_2N_6$ requires C, 42·1; H, 7·0%), and its *mono*-2 : 4-*dinitrophenylhydrazone*, m. p. 120° after crystallisation from ether–ligroin (b. p. 40—60°) (Found: C, 48·9; H, 5·1. $C_{15}H_{18}O_6N_4$ requires C, 48·9; H, 4·8%).

The α-diketone (7 g.), dissolved in dry ether (20 c.c.), was added dropwise with constant shaking to the Grignard compound obtained from magnesium (4·8 g.) and methyl iodide (29 g., 2·5 mols.) in ether (60 c.c.) cooled in a freezing mixture. The mixture was well shaken to cause reaction with an orange solid which separated to the top of the reaction mixture, refluxed for 1 hour, and left at room temperature overnight. The mixture was decomposed with ice and ammonium chloride and extracted with ether. After drying (K_2CO_3), the ether was removed through a column and the residue fractionally distilled. Two main fractions, b. p. 69—80°/24 mm. (3 g.) and b. p. 103—106°/23 mm. (3·5 g.), were obtained. The former is probably the *keto-carbinol* $CHMe_2{\cdot}CO{\cdot}CMe_2{\cdot}OH$ which forms a *semicarbazone*, m. p. 196° after crystallisation from alcohol (Found: C, 51·6; H, 9·2; N, 22·6. $C_8H_{17}O_2N_3$ requires C, 51·4; H, 9·1; N, 22·45%). The semicarbazone of the isomeric keto-carbinol $Me{\cdot}CO{\cdot}CMePr^i{\cdot}OH$ is stated (Locquin and Leers, *loc. cit.*) to have m. p. 134°. The higher-boiling fraction is the required diol. This (1·5 g.) was added, with good mechanical stirring, dropwise to concentrated sulphuric acid (12 g.) cooled in a freezing mixture. The mixture was allowed to warm to room temperature and was then poured on crushed ice, and the aqueous liquid was distilled. The ketone, of camphoraceous odour, readily distilled in steam and was obtained by ether-extraction of the first runnings of the distillate. Fractionation of the residue from the dried ethereal solution gave fractions, b. p. 64—75°/59 mm. and 74—78°/56 mm. The former gave the semicarbazone of 3 : 3 : 4-trimethyl-n-pentane-2-one (after dilution of the aqueous-alcoholic sodium acetate with water) which, after crystallisation from a concentrated solution in ether–ligroin (b. p. 40—60°), had m. p. 153° in agreement with that recorded by Locquin and Leers (*loc. cit.*). A mixture of this semicarbazone with that, m. p. 154°, of the ozonolysis ketone depressed the m. p. to 139—140°. The crystalline forms of the two semicarbazones, crystallised from the same solvent, are also quite different. The fraction, b. p. 74—78°/56 mm., probably the isomeric ketone $Pr^i{\cdot}CO{\cdot}CMe_2$, was not further investigated.

6-*Methyl-n-heptan-2-one* (3). *iso*Amyl iodide (14·8 g.) was added to the sodio-derivative of ethyl acetoacetate, prepared from 9·7 g. of the ester and 1·82 g. of sodium in 30 c.c. of absolute alcohol, and the reaction mixture was refluxed for 5·5 hours. Fractional distillation of the product, isolated in the usual manner, afforded, in addition to unchanged materials, ethyl *iso*amylacetoacetate (10 g.), b. p. 127—129°/23 mm. This keto-ester, with semicarbazide hydrochloride in aqueous-alcoholic sodium acetate, exhibited a behaviour which was observed with several branched-chain alkylacetoacetic esters. No precipitation of a semicarbazone occurred during 24—36 hours but dilution then precipitated a deep-blue oil which slowly gave colourless crystals of 1-*carbamyl*-3-*methyl*-4-*isoamylpyrazolone*, m. p. 157° after crystallisation from ether (Found: C, 56·5; H, 7·7; N, 19·3. $C_{10}H_{17}O_2N_3$ requires C, 56·9; H, 8·05; N, 19·9%).

Hydrolysis of ethyl *iso*amylacetoacetate was effected by refluxing with concentrated hydrochloric acid for 3 days. The mixture was diluted and distilled, the distillate was saturated with salt, and the ketone extracted with ether. It was converted directly into its semicarbazone, m. p. 153—155°, after crystallisation from alcohol (lit., m. p. 153°) (Found: C, 58·25; H, 10·1. Calc. for $C_9H_{19}ON_3$: C, 58·4; H, 10·3%). A mixture of this semicarbazone with that, m. p. 154°, of the ozonolysis ketone, had an indefinite m. p., 126—140°. The identity of the synthetic ketone was established by the preparation of its *p*-nitrophenylhydrazone, m. p. 82° (lit., m. p. 83°), and its 2 : 4-*dinitrophenylhydrazone*, m. p. 76° after crystallisation from ether–ligroin (b. p. 40—60°) (Found: C, 54·1; H, 6·3. $C_{14}H_{20}O_4N_4$ requires C, 54·5; H, 6·5%).

3 : 4-*Dimethyl-n-hexan-2-one* (4). This was prepared by the action of *sec.*-butyl bromide (12·3 g.) on the sodio-derivative obtained from sodium (2·05 g.) and absolute methyl alcohol (30 c.c.) on ethyl methylacetoacetate (11·6 g.). The resulting ethyl methyl-*sec.*-butylacetoacetate, b. p. 107—109°/20 mm., gave no colour with ferric chloride, and was hydrolysed directly with boiling concentrated hydrochloric acid for 24 hours. The product isolated as above contained a large amount of unhydrolysed ester but fractional distillation gave a small amount of a peppermint-smelling ketone, b. p. 65°/13 mm., which gave a *semicarbazone*, m. p. 141° after crystallisation from ether (Found: C, 57·8; H, 10·2. $C_9H_{19}ON_3$ requires C, 58·4; H, 10·3%). The ketone obtained by Powell and Secoy (*loc. cit.*) is described as probably a mixture of isomeric ketones, the semicarbazone of which had m. p. 124—126°. Admixture of the semicarbazone, m. p. 141°, with that, m. p. 154°, of the ozonolysis ketone depressed the m. p. to 124—138°.

3 : 5-*Dimethyl*-n-*hexan*-2-*one* (5). *iso*Butyl bromide (13·7 g.) was refluxed for 6 hours with the potassio-derivative of ethyl acetoacetate, from potassium (3·9 g.) and ethyl acetoacetate (13 g.) in alcohol (50 c.c.). Isolation of the product in the usual manner gave ethyl *iso*butylacetoacetate, b. p. 100—105°/12 mm., which was methylated to give ethyl methyl*iso*butylacetoacetate, b. p. 100—101°/9 mm., characterised as its *semicarbazone*, m. p. 108° after crystallisation from ether–ligroin (b. p. 40—60°) (Found: C, 55·8; H, 8·6. $C_{12}H_{23}O_3N_3$ requires C, 56·4; H, 9·3%). Hydrolysis of this with boiling concentrated hydrochloric acid for 12 hours gave a small yield of the required *ketone*, b. p. 67°/58 mm., of odour similar to, but rather less camphoraceous than, that of the ozonolysis ketone. Its *semicarbazone*, m. p. 115° after crystallisation from ether–ligroin (b. p. 40—60°) (Found: C, 58·0; H, 10·0. $C_9H_{19}ON_3$ requires C, 58·4; H, 10·3%), depresses the m. p. (154°) of the semicarbazone of the ozonolysis

ketone to 103—108°. Its 2 : 4-dinitrophenylhydrazone has m. p. 55° after crystallisation from a very concentrated solution in ligroin (b. p. 40—60°).

5-Methyl-n-heptan-2-one (6). 2-Methyl-n-butan-1-ol ("active" amyl alcohol) was converted by the action of phosphorus pentabromide at −5° into the bromide, b. p. 49°/62 mm., 45·3 g. of which were refluxed for 7—8 hours with the sodio-derivative from sodium (6·9 g.) and ethyl acetoacetate (39 g.) in dry ethyl alcohol (100 c.c.). The resulting *ethyl (2-methyl-n-butyl)acetoacetate*, b. p. 114·5°/14 mm., with semicarbazide acetate forms *1-carbamyl-3-methyl-4-(2-methyl-n-butyl)pyrazolone*, m. p. 156° after crystallisation from alcohol and then from ether (Found: C, 56·4; H, 7·7. $C_{10}H_{17}O_3N_3$ requires C, 56·9; H, 8·1%). The structure was confirmed by the following observations. It dissolved in *cold* aqueous sodium hydroxide and was reprecipitated unchanged (m. p. and mixed m. p.) on careful acidification. When it was refluxed with 2*N*-sodium hydroxide for 1 hour, ammonia was evolved. Acidification of the resulting solution at 0° with dilute hydrochloric acid caused precipitation of a white solid, with evolution of carbon dioxide. The acid was added dropwise until the precipitate just redissolved. Basification with sodium carbonate then precipitated *3-methyl-4-(2-methyl-n-butyl)pyrazolone*, m. p. 218° after crystallisation from aqueous alcohol (Found: C, 64·1; H, 9·7; N, 16·1. $C_9H_{16}ON_2$ requires C, 64·2; H, 9·6; N, 16·6%).

Prolonged (40 hours) hydrolysis of the acetoacetic ester with boiling concentrated hydrochloric acid gave *5-methyl-n-heptan-2-one*, b. p. 91°/55 mm. (Found: C, 74·4; H, 12·1. $C_8H_{16}O$ requires C, 75·0; H, 12·5%), which readily forms a *semicarbazone*, m. p. 138·5° after crystallisation from alcohol (Found: C, 58·2; H, 10·4. $C_9H_{19}ON_3$ requires C, 58·4; H, 10·3%), which depresses the m. p. of the ozonolysis semicarbazone to 110°. The *2 : 4-dinitrophenylhydrazone*, m. p. 67° (from ether–ligroin) (Found: C, 54·3; H, 6·5. $C_{14}H_{20}O_4N_4$ requires C, 54·5; H, 6·5%), depresses the m. p. (71°) of the corresponding derivative of (1) to 57—63°.

4-Methyl-n-heptan-2-one (7). This ketone was prepared but not characterised by Clarke (*loc. cit.*). *sec.*-Amyl bromide (45·3 g.) was refluxed for 6 hours with the sodio-derivative of ethyl acetoacetate (from 6·9 g. of sodium, and 39 g. of ethyl acetoacetate in 100 c.c. of dry ethyl alcohol) to give *ethyl sec.-amylacetoacetate*, b. p. 108°/10 mm. (Found: C, 66·0; H, 10·2. $C_{11}H_{20}O_3$ requires C, 66·0; H, 10·0%), which is readily hydrolysed by concentrated hydrochloric acid (24 hours) to give the ketone, b. p. 83°/47 mm. (Found: C, 75·4; H, 12·5. Calc. for $C_8H_{16}O$: C, 75·0; H, 12·5%). The *semicarbazone*, m. p. 108° after crystallisation from ether–ligroin (b. p. 40—60°) (Found: C, 58·1; H, 10·1. $C_9H_{19}ON_3$ requires C, 58·4; H, 10·3%), depresses the m. p. of the ozonolysis semicarbazone to 101° (indefinite). The 2 : 4-dinitrophenylhydrazone has m. p. 54° after crystallisation from ligroin (b. p. 40—60°).

3-Ethyl-n-hexan-2-one (8). This ketone has already been prepared, but not characterised (Clarke and Riegel, *loc. cit.*). Condensation of *n*-propyl bromide with the sodio-derivative of ethyl ethylacetoacetate gave ethyl ethyl-n-propylacetoacetate, b. p. 98°/10 mm., which gives no colour with ferric chloride (Found: C, 66·1; H, 10·0. Calc. for $C_{11}H_{20}O_3$: C, 66·0; H, 10·0%). With semicarbazide hydrochloride in saturated sodium acetate no precipitate is formed after several days, but dilution then precipitates an oil which crystallises overnight to yield the true *semicarbazone*, m. p. 104° after crystallisation from ether (Found: C, 56·2; H, 8·7. $C_{10}H_{21}ON_3$ requires C, 56·0; H, 9·9%).

Hydrolysis of the acetoacetic ester with boiling 50% sulphuric acid gives the ketone, b. p. 65—68°/56 mm., which slowly affords a *semicarbazone*, m. p. 81° (depressed to 70—80° by the ozonolysis semicarbazone), after crystallisation from ligroin (b. p. 40—60°) (Found: C, 58·8; H, 10·5. $C_9H_{19}ON_3$ requires C, 58·4; H, 10·3%). The *2 : 4-dinitrophenylhydrazone*, m. p. 62—64° (Found: C, 54·15; H, 6·35. $C_{14}H_{20}O_4N_4$ requires C, 54·5; H, 6·5%) after crystallisation from a very concentrated solution in ether–ligroin (b. p. 40—60°), also depresses the m. p. of the corresponding derivative of the ozonolysis ketone to 51—55°.

4-Methyl-3-ethyl-n-pentan-2-one (9) (Clarke, *loc. cit.*). This substance was similarly obtained from ethyl ethyl*iso*propylacetoacetate, b. p. 96°/10 mm. (Found: C, 65·7; H, 9·7. Calc. for $C_{11}H_{20}O_3$: C, 66·0; H, 10·0%). In agreement with Clarke this ester is extremely difficult to hydrolyse. By prolonged (4—5 days) hydrolysis with boiling aqueous potassium hydroxide a small amount of the ketone was obtained; it was converted directly into its *semicarbazone*, m. p. 121·5° after crystallisation from ligroin (b. p. 40—60°) containing a little ether (Found: C, 58·3; H, 10·2. $C_9H_{19}ON_3$ requires C, 58·4; H, 10·3%), which also depresses the m. p. of the ozonolysis derivative to 105—120°.

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THE UNIVERSITY, LEEDS. [*Received, February 15th*, 1950.]

265. *The Synthesis of 4-Carboxyvitamin-A Acid.*

By V. Petrow and O. Stephenson.

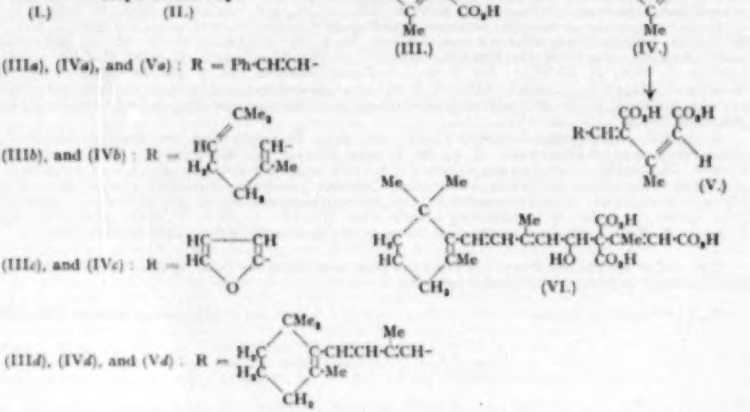
Condensation of cinnamaldehyde with ethyl (*cis* + *trans*)-β-methylglutaconate (II ; R′ = Et) yields trans-6-*phenyl*-2-*methylhexa*-1 : 3 : 5-*triene*-1 : 3-*dicarboxylic acid* (IIIa), converted by acetic anhydride into the anhydride (IVa), the constitution of which follows from its direct synthesis from β-methylglutaconic anhydride. The corresponding *cis*-*acid* (Va) is obtained by hydrolysis of (IVa), into which it reverts when heated. Similar *compounds* are obtained from citral and furfuraldehyde.

When β-ionylideneacetaldehyde (Id) is employed in the above condensation, trans-4-*carboxyvitamin-A acid* (IIId) is obtained, possessing slight vitamin-A activity which is increased after reduction of the compound with lithium aluminium hydride. The derived *anhydride* (IVd) is devoid of biological activity.

Attempts to convert 4-carboxyvitamin-A acid (IIId) into vitamin-A acid were unsuccessful.

The possibility of using β-methylglutaconic acid (II ; R′ = H) for the synthesis of polyenes, foreshadowed by Hurd and Abernethy (*J. Amer. Chem. Soc.*, **1941**, **63**, 976), has now been realised by the preparation of trans-4-*carboxyvitamin-A acid* [8-(2 : 6 : 6-*trimethylhex*-1-*en*-1-*yl*)-2 : 6-*dimethylocta*-1 : 3 : 5 : 7-*tetraene*-trans-1 : 3-*dicarboxylic acid*] (IIId) from β-ionylideneacetaldehyde (Id) (Arens and van Dorp, *Nature*, **1947**, **160**, 189 ; Dutch Patent 63015/1949) and (II ; R′ = Et). The experimental conditions obtaining for the condensation of the latter compound with aldehydes, however, required prior study for which cinnamaldehyde (Ia), citral (Ib), and furfuraldehyde (Ic) were employed.

Ethyl β-methylglutaconate (II ; R′ = Et) (*cis*- + *trans*-forms) failed to condense with cinnamaldehyde (Ia) in the presence of organic bases such as pyridine, or in acetic anhydride containing a trace of sulphuric acid. When the components were mixed in the presence of 6—8 equivalents of methanolic potassium hydroxide at 5°, however, reaction occurred to give, on acidification after 7 days, a 70% yield of 6-*phenyl*-2-*methylhexa*-1 : 3 : 5-*triene*-1 : 3-*di*-



carboxylic acid, m. p. 200°. The presence of two carboxy-groups in the compound was shown by the preparation of a *bis*-n-*butylamine* salt, whilst its triply unsaturated character was revealed by catalytic hydrogenation to the fully saturated 6-*phenyl*-2-*methyl*-n-*hexane*-1 : 3-*dicarboxylic acid*. When *cis*- or *trans*-β-methylglutaconic acid (II ; R′ = H) was employed in place of the mixture of ethyl esters, condensation only occurred in the presence of acetic anhydride at 100°, to give 6-*phenyl*-2-*methylhexa*-1 : 3 : 5-*triene*-1 : 3-*dicarboxylic anhydride* (IVa) in good yield. The constitution assigned to this compound followed from its preparation by condensation of

cinnamaldehyde with β-methylglutaconic anhydride in boiling benzene solution in the presence of pyridine. The same anhydride was also obtained by direct treatment of the diacid, m. p. 200°, with acetic anhydride (cf. Rogerson and Thorpe, *J.*, 1905, 1691). Alkaline hydrolysis of (IVa) furnished an isomeric *dicarboxylic acid*, which differed sharply from the product of m. p. 200° in its behaviour on heating, for smooth and spontaneous reversion to the anhydride (IVa) occurred. This observation leads to its formulation as *6-phenyl-2-methylhexa*-1 : 3 : 5-*triene*-cis-1 : 3-*dicarboxylic acid* (Va). The product, m. p. 200°, must therefore be assigned the alternative *trans*-1 : 3-constitution (IIIa). In accordance with these formulations, the absorption spectra of both (IIIa) and (Va) showed maxima at 313 mμ. with a slightly higher extinction coefficient in the case of the *trans*-acid (IIIa). The anhydride (IVa), in contrast, showed more intense absorption at a longer wave-length (see below).

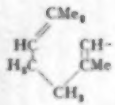
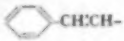
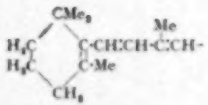
Condensation of ethyl (*cis* + *trans*)-β-methylglutaconate (II; R′ = Et) with citral (Ib) in the presence of methanolic potassium hydroxide leads to a good yield of a 2 : 6 : 10-*trimethylundeca*-1 : 3 : 5 : 9-*tetraene*-1 : 3-*dicarboxylic acid*, characterised by conversion into a *bis*-n-*butylamine* salt. A *trans*-configuration (IIIb) is tentatively assigned to this compound and is supported by the observation that the compound could not be converted into the corresponding *anhydride* (IVb), which was ultimately prepared in low yield from *cis*- or *trans*-β-methylglutaconic acid and citral in acetic anhydride. Furfuraldehyde (Ic) likewise gave 2-*methyl*-4-(2-*furyl*)*buta*-1 : 3-*diene*-trans-1 : 3-*dicarboxylic acid* (IIIc), readily converted into the *anhydride* (IVc) by treatment with acetic anhydride in ethyl acetate.

The reaction between ethyl (*cis* + *trans*)-β-methylgutaconate (II; R′ = Et) and β-ionylideneacetaldehyde (Id) in the presence of >3 equivalents of methanolic potassium hydroxide followed essentially the same pattern, the *dipotassium* salt of *trans*-4-carboxyvitamin-A acid being readily obtained in *ca.* 80% yield. The corresponding acid (IIId), characterised by conversion into the *bis*-n-*butylamine* and *bisisopropylamine* salts, rather surprisingly failed to give the Carr–Price reaction. Catalytic hydrogenation gave an oily *octahydro*-derivative. The deep-red *4-carboxyvitamin-A acid anhydride* (IVd) was prepared from β-ionylideneacetaldehyde and β-methylglutaconic anhydride in benzene, with pyridine as a catalyst, or by the carefully controlled action of acetic anhydride on (IIId). It differed from (IIId) in giving a ruby-red colour in the Carr–Price reaction. On hydrolysis it furnished the *cis*-acid (Vd), and on reaction with aniline a cis-*4-carboxyvitamin-A acid monoanilide* (cf. Rogerson and Thorpe, *loc. cit.*).

Neither (IIId) nor (IVd) proved suitable intermediates for conversion into vitamin A. Attempts to effect preferential decarboxylation of (IIId) by heating it with potassium or barium hydroxide, with alcoholic hydrochloric acid, or with pyridine or quinoline, under a variety of conditions, proved uniformly unsuccessful. Hydrogenation of the anhydride (IVd) to a phthalide type of structure likewise failed to give useful results. Reduction of *trans*-4-carboxyvitamin A (IIId) with 2·2 moles of lithium aluminium hydride, however, yielded a pale yellow gum which gave a strong mauve-blue colour with the Carr–Price reagent and had a vitamin A activity of *ca.* 2000 I.U./g.

Condensation of cinnamaldehyde with α-carboxy-β-methylglutaconic acid (cf. Fichter and Schwab, *Annalen*, 1906, **347**, 251; Feist, *ibid.*, **345**, 60) in the presence of hot methanolic potassium hydroxide gave 6-phenyl-2-methylhexa-1 : 3 : 5-triene-*trans*-1 : 3-dicarboxylic acid (IIIa) in low yield. β-Ionylideneacetaldehyde, under similar conditions, but after being kept for 6 days at room temperature, yielded an unstable compound which decomposed on attempted crystallisation and gave analytical figures in agreement with $C_{22}H_{36}O_7$. Although these figures correspond to a 4-hydroxy-8-(2 : 6 : 6-trimethyl*cyclo*hex-1-enyl)-2 : 6-dimethylocta-2 : 5 : 8-triene-1 : 3 : 3-tricarboxylic acid (VI), light-absorption data fail to support this formulation, the absorption maximum lying at 323 mμ., $\varepsilon_{max.}$ = 13,600 (in *cyclo*hexane), *i.e.*, at a much longer wave-length than may be expected for (VI) (cf. Braude, *Ann. Reports*, 1945, **42**, 115). A compound of structure (VI) is claimed by Milas in U.S.P. 2,369,158, who describes its decarboxylation and concomitant dehydration to vitamin-A acid. When our product was treated with pyridine under the conditions specified by the American authors decomposition invariably occurred, to give gummy mixtures which did not give positive Carr–Price reactions and are being assayed for vitamin A activity by Dr. S. W. F. Underhill and Miss B. M. Manley, B.Sc. (Physiological Department, The British Drug Houses, Ltd.), who will report it elsewhere.

Absorption Data.—The light absorptions of the various compounds described in this paper (for which the authors are indebted to Dr. R. E. Stuckey and Mr. P. Stross, B.Sc., Analytical Department, The British Drug Houses Ltd.), together with published values for the related polyenemonocarboxylic acids, are set out in the accompanying Table.

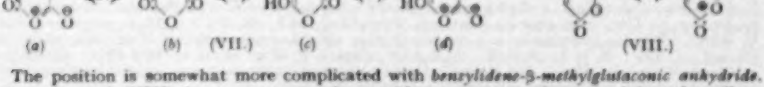
	R.	R'.	Monocarboxylic acid. $\lambda_{max.}$, mμ.	$\varepsilon_{max.}$	*trans*-Dicarboxylic acid. $\lambda'_{max.}$, mμ.	$\varepsilon_{max.}$	Anhydride. $\lambda''_{max.}$, mμ.	$\varepsilon_{max.}$	*cis*-Dicarboxylic acid. $\lambda'''_{max.}$, mμ.	$\varepsilon_{max.}$	$\lambda - \lambda'$.	$\lambda'' - \lambda'$.
(*A*)	Me·CH:CH-	H	303 *n*-H	37,000 [1]	—	—	—	—	—	—	—	—
(*B*)		H	—	—	271 *c*H	14,150	337·5 *i*P	19,300	—	—	—	—
(*C*)		H	—	—	279 *c*H	20,800	357 *i*P	27,930	—	—	24	78
(*D*)	Me·CH:CH·CH:CH-	H	332 *n*-H	49,000 [1]	—	—	—	—	—	—	—	—
(*E*)		H	—	—	313 *c*H	31,500	388 *c*H	38,900	313 *c*H	28,600	19	75
(*F*)		H	337 E	31,400 [1]	300 *i*P	29,300	386 *i*P	63,600	—	—	37	86
(*G*)		Me	343 E	44,700 [2]	320 *i*P	30,400	435 *c*H	34,000	327 W	19,640	23	115
Bis*iso*propylamine salt			—	—	333 (W)	29,000	—	—	—	—	—	—
Bisbutylamine salt			—	—	334 (W)	27,900	—	—	—	—	—	—

Solvents employed in absorption measurements: *c*H = *cyclo*hexane; E = ethanol; *n*-H = *n*-hexane; *i*P = *iso*propyl alcohol; W = water.

[1] Hausser, Smakula, Kuhn, and Hoffer, *Z. physiol. Chem.*, 1935, *B*, **29**, 371. [2] Hausser, Kuhn, Smakula, and Deutsch, *ibid.*, p. 378. [3] Arens and van Dorp, *Nature*, 1946, **157**, 190.

In passing from octatrienoic acid (*A*) to the model compound benzylidene-β-methylglutaconic acid (*B*), the absorption maximum was found to shift to a shorter wave-length while, at the same time, there was a pronounced lowering in the intensity. These changes could hardly be due to the additional carboxyl group present in the latter acid. A more fundamental structural difference was clearly involved and, in seeking to establish this factor, recourse was had to scale models, examination of which revealed the presence of steric inhibition in benzylidene-β-methylglutaconic acid (cf. Pauling, *Helv. Chim. Acta*, **1949**, **32**, 2241). Now steric interference, when sufficiently large, is known to decrease the planarity of a conjugated system, the energy content of the contributing resonance forms being thereby increased and the energy level of the excited state raised relatively to that of the ground state, *i.e.*, " the characteristic band itself will be displaced towards shorter wave-lengths " (Braude *et al.*, *J.*, **1949**, 1890) and will be less intense (Braude *et al.*, *ibid.*, p. 607). The same factors obtain in all the dicarboxylic acids prepared in this investigation. The absorption maxima (λ′) of (*C*), (*E*), (*F*), and (*G*) should therefore lie at shorter wave-lengths than those (λ) of their monocarboxylic acid analogues (*A*), (*D*), (*F*), and (*G*), and this is indeed found to be the case. Smaller values for $\varepsilon_{max.}$ were also observed as expected.

β-Methylglutaconic acid itself (II; R′ = H) may be regarded as a γ-carboxy-β-methylcrotonic acid. As crotonic acid in aqueous solution shows an absorption band at 200 mμ. ($\varepsilon_{max.}$ = 10,000) (Mohler and Lohr, *Helv. Chim. Acta*, **1938**, **21**, 485), its γ-carboxy-derivative (II) should likewise show an absorption band at *ca.* 200 mμ. (cf. Morton, *Ann. Reports*, **1941**, **38**, 18; Braude, *ibid.*, **1945**, **42**, 112). Actually selective absorption was not observed with either *cis*- or *trans*-β-methylglutaconic acid at wave-lengths greater than 220 mμ. β-Methylglutaconic anhydride, however, showed a maximum at 327 mμ., $\varepsilon_{max.}$ = 6050 (in *cyclo*hexane), *i.e.*, conversion of (II; R′ = H) into the anhydride had led to the appearance of a band at a much longer wave-length. This is hardly surprising as the anhydride of (II) is in reality a pyrone derivative (Bland and Thorp, *J.*, **1912**, 856) which exists as a resonance hybrid derived from the canonical forms (VIIa—*d*) (cf. Cavalier, *Chem. Reviews*, **1947**, **41**, 525).



The position is somewhat more complicated with *benzylidene-β-methylglutaconic anhydride*. This compound (VIII) bears a structural resemblance to a *p*-quinone and is pale yellow. Replacement of the phenyl group in (VIII) by a more extended conjugated system produces the expected increase in $\lambda_{max.}$ and $\varepsilon_{max.}$, accompanied by a corresponding bathochromic effect, the anhydrides (*E*) and (*F*) being orange-yellow. Further lengthening of the conjugated chain produces a further increase in $\lambda_{max.}$ and a deepening in colour, the anhydride (*G*) being bright red, but it does not leads in this instance to a further increase in $\varepsilon_{max.}$. This result falls into line with the earlier observations of Buroway (*J.*, **1941**, 20) and Braude *et al.* (*J.*, **1949**, 1890) on the abnormal light-absorption properties of the β-ionone residue with its relatively low values for $\varepsilon_{max.}$ which are apparently due to the " steric hindrance effect " (Braude, *loc. cit.*).

Only one *cis*-acid, (*E*), was obtained pure. Its light absorption supports its structure, the value for $\lambda_{max.}$ being the same for both isomers, and $\varepsilon_{max.}$ slightly higher for the more linear *trans*-dicarboxylic acid (cf. Braude, *loc. cit.*).

Experimental.

(M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.)

6-Phenyl-2-methylhexa-1 : 3 : 5-triene-trans-1 : 3-dicarboxylic Acid (IIIa).—To a solution of potassium hydroxide (43 g.) in methanol (300 ml.) at −20° was added a mixture of ethyl (*cis* + *trans*)-β-methylglutaconate (22·5 g.) and cinnamaldehyde (13·2 g.) in methanol (25 ml.) cooled to the same temperature. The mixture was then kept for 1 hour at −20° and stored at 0—5° for 7 days. The potassium salt was collected and acidified, and the product (18·5 g.; m. p. 190—194°) recrystallised from aqueous methanol giving *6-phenyl-2-methylhexa-1 : 3 : 5-triene-trans-1 : 3-dicarboxylic acid*, bright yellow needles (16 g.), m. p. 199—200° (decomp.) (Found : C, 69·4; H, 5·4. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·5%).

The *bis-n-butylamine* salt, white needles, m. p. 141—142°, from ethyl acetate containing a trace of methanol (Found : C, 67·6; H, 8·7; N, 6·6. $C_{23}H_{40}O_4N_2$ requires C, 68·3; H, 9·0; N, 6·9%), was obtained when a methanolic solution of the foregoing acid was treated with a slight excess of *n*-butylamine.

6-*Phenyl*-2-*methyl*-n-*hexane*-1 : 3-*dicarboxylic acid*, white needles, m. p. 109°, from ethyl acetate–light petroleum (b. p. 80—100°) (Found : C, 68·6; H, 7·6. $C_{13}H_{16}O_4$ requires C, 68·2; H, 7·6%), was obtained when a solution of the foregoing acid (2 g.) in ethyl acetate (200 ml.) was completely hydrogenated in the presence of palladium black (0·5 g.), six equivalents of hydrogen being absorbed.

6-*Phenyl*-2-*methylhexa*-1 : 3 : 5-*triene*-1 : 3-*dicarboxylic Anhydride* (IVa).—(*a*) A solution of β-methylglutaconic anhydride (7 g.) in benzene (100 ml.) was treated with cinnamaldehyde (7·35 g.), followed by pyridine (3 drops), and the mixture heated under reflux for 3 hours, whereupon the colour changed slowly from pale orange to deep red. Deposition of solid began after *ca.* 1 hour. After the mixture had cooled, the product [10 g.; m. p. 168—176° (decomp.)] was collected, washed with cold methanol, and crystallised from benzene or ethyl acetate. **6-*Phenyl*-2-*methylhexa*-1 : 3 : 5-*triene*-1 : 3-*dicarboxylic anhydride*** formed small orange-yellow plates, m. p. 180° (decomp.) (Found : C, 75·4; H, 4·9. $C_{13}H_{10}O_3$ requires C, 75·0; H, 5·0%).

(*b*) β-Methylglutaconic acid (*cis*- or *trans*-) (4·8 g.) was dissolved in warm acetic anhydride (20 ml.), and cinnamaldehyde (8·8 g.) in acetic anhydride (5 ml.) added. The cherry-red solution was heated on the water-bath for 4 hours, solids beginning to separate after *ca.* 1 hour. After the mixture had cooled, the product (7 g.; m. p. 164—174°) was collected and crystallised from benzene, yielding (IVa), m. p. 178—179° (decomp.), not depressed on admixture with a sample prepared by method (*a*).

(*c*) The acid (IIIa) (1 g.), dissolved in acetic anhydride (10 ml.), was warmed on the steam-bath for 1 hour. The cooled solution was diluted with methanol and the product recrystallised from benzene giving (IVa) (0·65 g.), m. p. 180° (decomp.), alone or on admixture with an authentic specimen.

6-*Phenyl*-2-*methylhexa*-1 : 3 : 5-*triene*-*cis*-1 : 3-*dicarboxylic Acid* (Va).—The foregoing anhydride (IVa) (2·3 g.) was suspended in water (100 ml.) containing potassium hydroxide (5 g.), and the mixture heated on the steam-bath for 2 hours. Solution was complete in *ca.* 20 minutes. The cooled mixture was carefully acidified with hydrochloric acid, unchanged material [0·15 g.; m. p. 178—180° (decomp.)] being recovered. The filtrate, on further dilution, gave the yellow crystalline *cis*-1 : 3-***dicarboxylic acid***, which was purified from methanol (Found : C, 69·7; H, 5·7. $C_{13}H_{12}O_4$ requires C, 69·8; H, 5·5%). The substance dehydrated on heating, finally melting with decomposition at the same temperature as the original anhydride (IVa). The bis-n-butylamine salt, m. p. 119° (frothing) after three recrystallisations from ethyl acetate–methanol, was very hygroscopic and a satisfactory analysis could not be obtained.

2 : 6 : 10-*Trimethylundeca*-1 : 3 : 5 : 9-*tetraene*-trans-1 : 3-*dicarboxylic Acid* (IIIb).—Ethyl β-methylglutaconate (20 g.) was added to a solution of potassium hydroxide (33·6 g.) in methanol (300 ml.) at 0°. After 5 minutes citral (15·2 g.) was added and the mixture warmed on the water-bath. Rapid separation of a crystalline potassium salt occurred in about 15 minutes and appeared to be complete after 30 minutes. After being kept overnight the potassium salt (20 g.) was collected. Water (2 ml.) was then added to the methanolic mother-liquors, and the solution boiled for 15 minutes and allowed to cool. A further quantity (6·5 g.) of potassium salt separated and was removed. A third crop (4·2 g.) of less pure material was obtained by concentration of the aqueous-methanolic mother-liquors. When the potassium salt (20 g.) was dissolved in water (200 ml.) and the cooled solution carefully acidified, **2 : 6 : 10-*trimethylundeca*-1 : 3 : 5 : 9-*tetraene*-trans-1 : 3-*dicarboxylic acid*** was obtained; it formed small needles, m. p. 148°, from aqueous methanol (Found : C, 68·8; H, 7·7. $C_{18}H_{28}O_4$ requires C, 69·0; H, 8·0%). The *bis-n-butylamine* salt separated from ethyl acetate–methanol in crystals, m. p. 117° (Found : C, 67·2; H, 10·2; N, 6·03. $C_{34}H_{64}O_4N_2$ requires C, 67·9; H, 10·4; N, 6·6%). Attempts to convert the dicarboxylic acid into the anhydride by treatment with acetic anhydride under a variety of conditions proved unsuccessful, intractable tars being obtained.

2 : 6 : 10-*Trimethylundeca*-1 : 3 : 5 : 9-*tetraene*-1 : 3-*dicarboxylic Anhydride* (IVb).—Citral (3·8 g.) and either *cis*- or *trans*-β-methylglutaconic acid (3·6 g.) dissolved in warm acetic anhydride (20 ml.) were heated on the water-bath for 3½ hours. The product obtained by decomposition of the mixture with aqueous ethanol yielded the ***anhydride***, buff-coloured needles, m. p. 110°, from ethyl acetate–light petroleum (b. p. 80—100°) (Found : C, 73·5; H, 7·6. $C_{18}H_{26}O_3$ requires C, 73·9; H, 7·8%).

2-*Methyl*-4-(2-*furyl*)*buta*-1 : 3-*diene*-trans-1 : 3-***dicarboxylic Acid*** (IIIc).—Ethyl β-methylglutaconate (20 g.) was added to a solution of potassium hydroxide (33·6 g.) in methanol (330 ml.), followed, after 10 minutes, by a solution of furfuraldehyde (9·6 g.) in methanol (15 ml.). The product was collected after 3 days at room temperature and, on acidification and ether extraction, yielded (73%) **2-*methyl*-4-(2-*furyl*)*buta*-1 : 3-*diene*-trans-1 : 3-*dicarboxylic acid***, small needles from hot water, m. p. 212° (decomp.) (Found : C, 59·1; H, 4·7. $C_{11}H_{10}O_5$ requires C, 59·4; H, 4·5%).

2-*Methyl*-4-(2-*furyl*)*buta*-1 : 3-*diene*-1 : 3-***dicarboxylic anhydride*** (IVc) separated in orange-yellow plates (1·3 g.), m. p. 138° (Found : C, 65·0; H, 4·1. $C_{11}H_8O_4$ requires C, 64·7; H, 4·0%), when light petroleum (b. p. 60—80°) was added to the mixture obtained by refluxing the foregoing acid (2 g.), ethyl acetate (30 ml.), and acetic anhydride (5 ml.) for 1 hour.

trans-4-*Carboxyvitamin-A Acid* (IIId).—β-Ionylideneacetaldehyde (Arens and van Dorp, *loc. cit.*) (13·08 g.) and ethyl β-methylglutaconate (12·0 g.) in methanol (5 ml.) were added to a solution of potassium hydroxide (20·16 g.) in methanol (125 ml.), and the mixture was heated to 60°. Rapid separation of solids began after 5 minutes and appeared to be complete after 35 minutes. After being kept overnight the *dipotassium* salt (21 g., 80%) of *trans*-4-carboxyvitamin-A acid was collected and dried at 90° (Found : C, 58·5; H, 6·3; K, 17·5. $C_{21}H_{34}O_4K_2,\frac{1}{2}H_2O$ requires C, 58·7; H, 6·3; K, 18·2%). The free *acid* separated from aqueous methanol in small yellow needles, m. p. 203—205° (decomp.) (Found : C, 72·8; H, 8·1. $C_{21}H_{30}O_4$ requires C, 73·2; H, 8·7%). The *bis-n-butylamine* salt separated from methanol–ethyl acetate in white crystals, m. p. 170° (decomp.) (Found : C, 70·9; H, 10·3; N, 5·7. $C_{29}H_{50}O_4N_2$ requires C, 71·0; H, 10·3; N, 5·7%). The *bis-isopropylamine* salt had m. p. 176° (decomp.) (Found : C, 69·6; H, 10·0; N, 5·8. $C_{27}H_{46}O_4N_2$ requires C, 70·1; H, 10·0; N, 6·1%). On catalytic hydrogenation in absolute ethanol in presence of platinum oxide, 1·72 g. of the acid absorbed 467 ml. of hydrogen (4[H] = 448 ml.), to give a gummy *product* which failed to crystallise (Found : C, 70·9; H, 10·1. $C_{21}H_{34}O_4$ requires C, 71·5; H, 10·3%).

When β-ionylideneacetaldehyde (4·77 g.) was treated with ethyl β-methylglutaconate (4·4 g.) in the

presence of piperidine acetate (8 drops), and the mixture left at room temperature for 10 days, a dark reddish-brown oil was obtained which, after stripping at 0·05 mm. from unchanged ester (4·2 g.) and aldehyde (1·53 g.), appeared to be the *aldol* (Found: C, 82·0; H, 9·7. $C_{29}H_{44}O_2$ requires C, 82·6; H, 10·2%) (yield, 2·3 g.). The compound gives a deep-blue colour with the Carr–Price reagent.

4-Carboxyvitamin-A Acid Anhydride (IVd).—(*a*) Addition of pyridine (1 ml.) to a hot solution of β-ionylideneacetaldehyde (15·9 g. of 65% aldehyde content) and β-methylglutaconic anhydride (6·3 g.) in benzene (20 ml.) led to an exothermic condensation, completed by heating the mixture for 1 hour under reflux. *4-Carboxyvitamin-A acid anhydride* (9 g.) was obtained from the viscous residue, and formed dark red needles, m. p. 126°, from light petroleum (b. p. 60—80°) (Found: C, 77·0; H, 7·7. $C_{21}H_{24}O_3$ requires C, 77·3; H, 8·1%). Hydrolysis with aqueous potassium hydroxide furnished the yellow *cis*-acid which reverted spontaneously to the anhydride on warming.

(*b*) When *trans*-4-carboxyvitamin-A acid was warmed for 10—15 minutes with a 10% solution of acetic anhydride in benzene, ethyl acetate, or alcohol, quantitative conversion into the dark red anhydride occurred, it being identified by m. p. and mixed m. p. with a sample prepared by method (*a*). When acetic anhydride alone was employed some decomposition occurred on heating, but slow conversion into the anhydride took place even at room temperature.

(*c*) When the anhydride (0·5 g.) was heated with aniline (1 ml.) and benzene (10 ml.) under reflux for 10 minutes, *cis*-*4-carboxyvitamin-A acid monoanilide* was obtained; it formed small orange needles, m. p. 158°, from aqueous methanol (decomp.) (Found: C, 76·8; H, 7·6; N, 3·5. $C_{27}H_{33}O_2N$ requires C, 77·3; H, 7·9; N, 3·3%).

Reduction of 4-Carboxyvitamin-A Acid with Lithium Aluminium Hydride.—A cooled solution of 4-carboxyvitamin A acid (1·72 g.) in absolute ether (250 ml.) was slowly treated with a solution of lithium aluminium hydride (0·42 g., 2·2 mols.) in ether (30 ml.), a vigorous reaction occurring. The mixture was heated under reflux for 30 minutes, whereupon the solid which had separated in the early stages of the reaction disappeared. The cooled mixture was carefully decomposed with ice, dilute sulphuric acid added, and the *product* present in the ethereal layer isolated as a pale yellow gum (Found: C, 76·2; H, 9·7. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·2%). The absorption (in *cyclo*hexane) gave a maximum at 303 mμ., $E^{1\%}_{1cm.}$ = 690.

Ethyl α-Carbethoxy-β-methylglutaconate Condensations.—(*a*) The tri-ester (27·2 g.) was added in one portion to an ice-cold solution of potassium hydroxide (33·6 g.) in methanol (300 ml.), followed by a solution of cinnamaldehyde (13·2 g.) in methanol (25 ml.). After being heated under reflux for 30 minutes the mixture was cooled and the potassium salt which had separated was collected. On acidification of its solution, carbon dioxide was evolved and 6-phenyl-2-methylhexa-1 : 3 : 5-triene-*trans*-1 : 3-dicarboxylic acid (4·4 g.) was precipitated, identified by m. p. and mixed m. p. with an authentic specimen.

(*b*) When the above reaction was carried out at room temperature for 3 days, acidification of the resultant potassium salt yielded a non-crystallisable gum which was converted into 6-phenyl-2-methylhexa-1 : 3 : 5-triene-*trans*-1 : 3-dicarboxylic acid by decarboxylation with boiling aqueous-alcoholic potassium hydroxide.

(*c*) β-Ionylideneacetaldehyde (6·54 g.) and the tri-ester (8·16 g.) in ethanol (20 ml.) at −10° were added to a cooled solution of potassium hydroxide (6·72 g.) in ethanol (60 ml.). After 6 days at room temperature the deposited potassium salt was collected, washed with cold ethanol until colourless, dissolved in water (100 ml.), and carefully acidified with hydrochloric acid at 0°. The precipitated solids were removed in ether at <30°, giving a *solid*, m. p. *ca.* 80° (decomp.) (Found: C, 65·0; H, 7·8. $C_{32}H_{50}O_7$ requires C, 65·0; H, 7·5%), which gave a trace of mauve colour with the Carr–Price reagent, probably due to an impurity. Decarboxylation experiments using pyridine gave products consisting largely of unchanged material (*e.g.*: Found: C, 67·8; H, 7·8%). Similar results were obtained on using quinoline, the product (Found: C, 71·9; H, 8·9%) obtained after 3 hours' heating in quinoline–ether having an absorption maximum (in *iso*propyl alcohol) at 330 mμ., $E^{1\%}_{1cm.}$ = 505.

Benzylidene-β-methylglutaconic Acid (cf. Feist and Beyer, *Annalen*, 1906, **345**, 125).—A mixture of benzaldehyde (10·6 g.) and β-methylglutaconic ester (20·0 g.) was added to a cooled solution of potassium hydroxide (16·8 g.) in methanol, and the mixture left at room temperature for 2 days. The potassium salt was collected and dissolved in water (50 ml.), and the solution acidified with hydrochloric acid. The product was washed with cold water and recrystallised from water containing a little ethanol, yielding needles of *benzylidene-β-methylglutaconic acid* (6 g.), m. p. 180° (decomp.) (Found: C, 67·3; H, 5·4. Calc. for $C_{13}H_{12}O_4$: C, 67·2; H, 5·2%) (Feist and Beyer, *loc. cit.*, give m. p. 169°).

Benzylidene-β-methylglutaconic Anhydride.—A suspension of the foregoing acid (0·8 g.) was heated under reflux with acetyl chloride (5 ml.), solution occurring in about 15 minutes. After a further 3 hours excess of acetyl chloride was distilled off, and the residue dissolved in ethyl acetate (10 ml.) and again evaporated to dryness. The residue on crystallisation from ethyl acetate–light petroleum (b. p. 80—100°) yielded *benzylidene-β-methylglutaconic anhydride* (700 mg.), shining yellow plates, m. p. 114—116° (Found: C, 72·8; H, 4·6. $C_{13}H_{10}O_3$ requires C, 72·9; H, 4·7%).

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RESEARCH LABORATORIES, THE BRITISH DRUG HOUSES LTD.,
LONDON, N.1.

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266. *Infra-red Spectroscopic Studies of the Structure of Molecular Complexes.*

By W. R. Burton and R. E. Richards.

The infra-red spectra of some molecular complexes and their pure components have been studied in the solid state and in solution. It is shown that two factors affect the stability of these complexes. The attraction factor largely determines the stability of complexes which exist in solution as well as in the solid state, but the packing factor accounts predominantly for the stability of some complexes which occur only in the solid state.

Abundant evidence has been obtained in recent years, mainly from *X*-ray measurements (*e.g.*, Powell and Huse, *J.*, 1943, 435; Powell, Huse, and Cooke, *J.*, 1943, 153; Saunder, *Proc. Roy. Soc.*, 1946, *A*, **188**, 1) that the constituents of molecular complexes formed between polar molecules such as picric acid, trinitrobenzene, and tricyanobenzene and polarisable molecules such as certain amines and hydrocarbons, are not held together by a normal chemical bond. Theories have been suggested by Briegleb (*Z. physikal. Chem.*, 1935, *B*, **31**, 58) and Pauling (*Proc. Nat. Acad. Sci.*, 1939, **25**, 577) which give explanations of much of the experimental data. During infra-red measurements on certain molecular complexes, however, we have found, as pointed out by Rapson, Saunder, and Stewart (*J.*, 1946, 1110), that these theories alone do not satisfactorily explain the properties of all these substances.

Experimental.—The complexes studied were very kindly supplied by Dr. Stewart of Capetown University, except the complex of dimethylaniline and *s*-trinitrobenzene, which was prepared by mixing a hot solution of *s*-trinitrobenzene in alcohol with hot dimethylaniline. The crystals which were deposited on cooling had m. p. 108° (Hepp, *Annalen*, 1882, **215**, 344).

Two infra-red spectrometers were used; in the region 15 to 6 μ. a single-beam instrument with a rock-salt prism (Whiffen and Thompson, *J.*, 1945, 268) and from 6 to 2 μ. a double-beam spectrometer with fluorite prism (Thompson, Whiffen, Richards, and Temple, Report 17, Hydrocarbon Group, Institute of Petroleum). The spectra of solids were studied both by the Nujol method (Richards, *J.*, 1947, 978) and by allowing the solid to crystallise from the melt between two rock-salt plates. Solutions were studied in the usual kind of absorption cell.

Results.—The spectra of typic compleaxes measured are shown with the spectra of their pure components in Figs. 1, 2, and 3. The 3 : 1-complex of *pp'*-dinitrodiphenyl and diphenyl (complex *A*) has an absorption spectrum corresponding to simple addition of the spectra of its components, except in the region 750—850 cm.$^{-1}$, where some of the bands occur at different frequencies. These bands are due to the out of plane vibrations of the C–H links of the benzene rings. Similar small shifts in these absorption bands are observed in the 3 : 1-complex of *pp'*-dinitrodiphenyl with *p*-hydroxydiphenyl (complex *B*). The strong band near 3 μ., which corresponds to the stretching vibration of the O–H link of *p*-hydroxydiphenyl, appears to be sharper in the molecular compound than in the pure material. This is reminiscent of the effect of intra-molecular hydrogen bonding, which usually causes the corresponding band to be sharper than is the case with inter-molecular hydrogen bonding. A small, though quite definite, peak appears at 1763 cm.$^{-1}$ in the complex, which is not present in either component, and the interpretation of which is unknown. In contrast to these two examples, the spectrum of the 1 : 1-complex of *s*-trinitrobenzene and dimethylaniline (complex *C*) differs very considerably from the spectra of its constituents.

Further information is obtainable from measurement of the intensities of certain absorption bands. If a band occurs in the spectrum of a component of a molecular compound in a region where there is no absorption by the other component, by the molecular compound, or by the solvent, the peak height of this band, previously calibrated by measuring solutions of the pure constituent of known strength, will serve as a measure of its concentration in a solution of a mixture. In the system *p*-hydroxydiphenyl–*pp'*-dinitrodiphenyl in acetone, the band at 766 cm.$^{-1}$ may be used to characterise the *p*-hydroxydiphenyl, since the corresponding bands of *pp'*-dinitrodiphenyl and the complex occur at 788 and at 777 cm.$^{-1}$, respectively. The results obtained with this mixture are shown in the table.

Actual concn. of *pp'*-dinitrodiphenyl (moles/ml.), $\times 10^4$	0·9	1·2	2·1
Actual concn. of *p*-hydroxydiphenyl (moles/ml.), $\times 10^4$	0·8	1·6	2·2
Concn. of *p*-hydroxydiphenyl deduced from peak height, $\times 10^4$	0·9	1·7	2·25

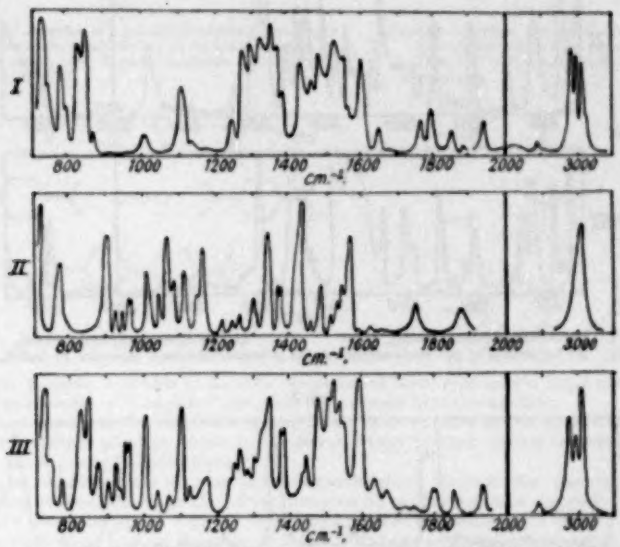
The presence of *pp'*-dinitrodiphenyl does not decrease the free *p*-hydroxydiphenyl concentration as would be expected if the complex existed in solution. Although the estimation of the *p*-hydroxydiphenyl can only be considered to be very approximate in view of the proximity of other bands, the results clearly indicate that complex formation in this solution can occur only to a very small extent, if at all.

Similar measurements on the system acenaphthene–*m*-dinitrobenzene in bromoform solution showed appreciable complex formation, since the concentrations of *m*-dinitrobenzene and acenaphthene, as measured from the peak heights of the bands at 787 and 808 cm.$^{-1}$, were always considerably less than the concentrations expected from the amounts of these compounds put into the solution. Although quantitatively the results were only very approximate, they suggested the formation in solution of a complex of the 1 : 1-type. The existence of a complex in solution is also indicated by the yellow colour

formed on mixing the constituents in solution (see von Halban and Zimpelmann, *Z. physikal. Chem.*, 1925, **117**, 461).

Discussion.—In complexes *A* and *B* it seems clear that the interaction between the polar and polarisable components is very small, if not absent. Indeed, much greater shifts of frequencies than were recorded in the formation of these complexes are often observed during changes of state in pure compounds (see, for example, Breit and Salant, *Physical Rev.*, 1930, **36**, 871; Hettner, *Z. Physik*, 1937, **107**, 549; Halford and Carpenter, *J. Chem. Physics*, 1947, **15**, 99; Richards and Thompson, *J.*, 1947, 1260; *Proc. Roy. Soc.*, 1948, *A*, **195**, 1). The absence of the complex *B* in solution, as deduced from the intensity measurements, also implies that the intermolecular attraction must be weak.

FIG. 1.



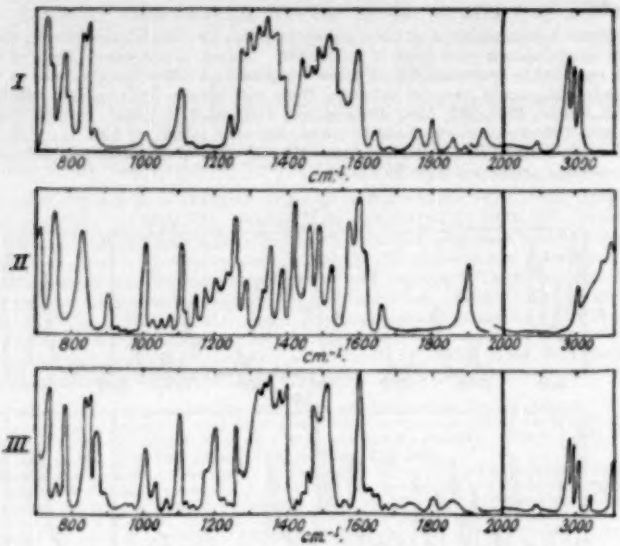
I. pp'-*Dinitrodiphenyl* (*solid*). II. *Diphenyl* (*solid*).
III. 3 : 1-*Complex of* pp'-*dinitrodiphenyl and diphenyl* (*complex A*) (*solid*).

The structure of complex *C* is probably of the alternating-layer type (Briegleb, *loc. cit.*). On the Briegleb theory, the bonds of the dimethylaniline possess dipole moments induced by the *s*-trinitrobenzene, and we should therefore expect frequency shifts in the spectrum of the dimethylaniline due to the changed polarity of the bonds. On the Pauling theory (Pauling, *loc. cit.*), one would expect the frequencies of the *s*-trinitrobenzene molecules also to be altered when it forms such a complex. The spectrum of complex *C*, showing considerable shifts in the frequencies of both components, is consistent with interactions of both the Briegleb and the Pauling type.

The infra-red studies so far therefore confirm that although the theories of Briegleb and Pauling can provide an explanation of the formation of some molecular complexes, these theories are not satisfactory in explaining the properties of the complexes of types *A* and *B* described above. There is no evidence of any strong forces of attraction between the components of these complexes, but at the same time their existence implies that their crystals must be more stable than those of the separate components.

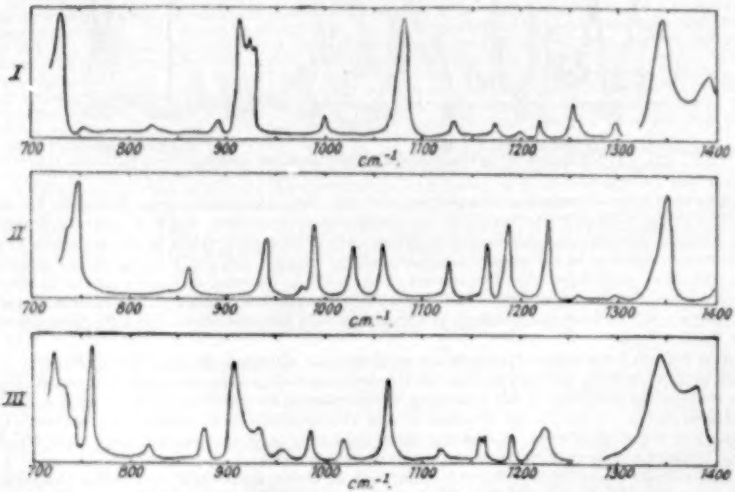
The marked dependence of the molecular ratio on the geometrical shapes of the components (Saunder, *loc. cit.*) suggests the importance of a packing factor. The reason for this can be understood if one assumes that these aromatic compounds prefer to crystallise in layer-type

FIG. 2.



I. pp'-*Dinitrodiphenyl* (*solid*). II. p-*Hydroxydiphenyl* (*solid*).
III. 3 : 1-*Complex of* pp'-*dinitrodiphenyl and* p-*hydroxydiphenyl* (*complex B*) (*solid*).

FIG. 3.



I. s-*Trinitrobenzene* (*solid*). II. *Dimethylaniline* (*liquid*).
III. 1 : 1-*Complex of* s-*trinitrobenzene and dimethylaniline* (*complex C*) (*solid*).

lattices. Fig. 4 shows diagrammatically the arrangement of the molecules in a crystal of the 3 : 1 molecular complex of *pp'*-dinitrodiphenyl and diphenyl (Saunder, *loc. cit.*; Rapson, Saunder, and Stewart, *J.*, 1946, 1110). A similar complex can be formed from dinitrodiphenyl and *NNN'N'*-tetramethylbenzidine, so it follows that from size considerations alone it should be possible for the pure dinitrodiphenyl to crystallise in a similar lattice to those of its complexes, as is shown in Fig. 5. It can be seen, however, that the oxygen atoms of the nitro-groups, which carry fractional negative charges, approach relatively closely to one another, and this would cause considerable repulsion between these nitro-groups. Pure *pp'*-dinitrodiphenyl does not therefore crystallise in this way, but forms a complicated lattice in which the nitro-groups overlap as far as possible in order to produce attraction instead of repulsion (Van Nickerk, *Proc. Roy. Soc.*, 1943, *A*, 181, 314). When allowed to crystallise in the presence

FIG. 4.

Structure of complex A : pp'-dinitrodiphenyl molecules are denoted by black circles, the diphenyl molecule by plain circles (see Rapson, Saunder, and Stewart, *J.*, 1946, 1110).

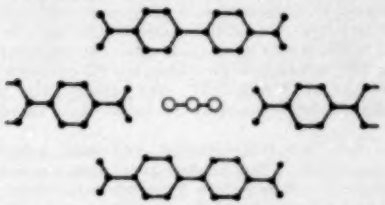
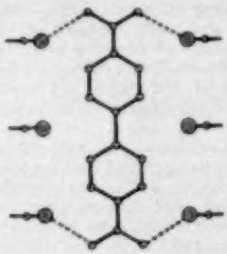


FIG. 5.

Showing repulsion between O-*atoms in a hypothetical crystal of* pp'-*dinitrodiphenyl of the same structure as its complexes.*



of diphenyl, however, it is able to do so in the preferred layer-type lattice, using the diphenyl molecules to separate or " insulate " the polar nitro-groups from one another.

It is concluded that the complexes *A* and *B* owe their stability not to forces of attraction between the components but rather to the lower energy of their crystal lattices compared with that of the pure *pp'*-dinitrodiphenyl.

When, in addition to the packing factor discussed above, there is also some definite force of attraction between the molecules of the components of the molecular complex, one would expect more than one type of complex to be formed, depending upon which of the two factors finally predominates. As an example, if *NNN'N'*-tetramethylbenzidine is added to a hot solution of *pp'*-dinitrodiphenyl, a 1 : 4-complex separates on cooling, whereas on adding *pp'*-dinitrodiphenyl to excess of tetramethylbenzidine a 1 : 1-complex separates immediately (Rapson, Saunder, and Stewart, *loc. cit.*; see also Sudborough and Bear, *J.*, 1910, 97, 773; Sudborough, *J.*, 1916, 109, 1339).

In conclusion we thank Dr. Stewart of Capetown University, for the provision of samples of molecular complexes, and Dr. H. W. Thompson, F.R.S., for the use of the spectroscopic equipment.

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267. *Esters Containing Phosphorus. Part X. Radioactive Diisopropyl Fluorophosphonate (D.F.P.).*

By B. C. Saunders and T. S. Worthy.

Radioactive diisopropyl fluorophosphonate has been prepared from phosphorus containing ^{32}P. A description is given of a specially designed apparatus which enables an overall yield of 62% to be obtained.

We have previously given details of the preparation of diisopropyl fluorophosphonate (I) (McCombie and Saunders, *Nature*, 1946, **157**, 287; Saunders *et al.*, B.P. 601,210; Saunders and Stacey, *J.*, 1948, 695) according to the scheme:

$$PCl_3 + 3HOPr^i \longrightarrow P(OPr^i)_3 \xrightarrow{HCl} P(OH)(OPr^i)_2 + PrCl \xrightarrow{Cl_2} O{:}PCl(OPr^i)_2 \xrightarrow{NaF} O{:}PF(OPr^i)_2 \quad (I.)$$

Reference was made in the above papers to the remarkable physiological properties of (I), including its miotic action, clinical applications in connexion with glaucoma and paralytic ileus, and to its powerful anti-cholinesterase activity. Towards cholinesterase it was effective in concentrations as low as 10^{-11} M. In order to throw light on its mode of action with esterases (see Boursnell and Webb, *Nature*, 1949, **164**, 875) radioactive (I) containing ^{32}P has been prepared (cf. our preliminary announcement, *Nature*, 1949, **163**, 797). The present paper gives a detailed account of its production on what may conveniently be called the "one-gram scale."

Phosphorus containing ^{32}P was obtained from A.E.R.E., Harwell, and small quantities (of the order of 1 g.) were converted into the trichloride. This small-scale conversion presented considerable and unexpected difficulties, the most serious feature being the very ready production of phosphorus pentachloride. [All the reliable descriptions of the preparation of phosphorus trichloride are on a basis of *ca.* 200 g. of phosphorus (cf. *Inorg. Synth.*, **2**, 145).] This tendency to pentachloride formation was checked by the correct geometry of the apparatus and by the method of manipulation.

The active trichloride was converted into diisopropyl hydrogen phosphite and thence through the chlorophosphonate into the fluorophosphonate essentially according to the scheme shown above, although a modified apparatus and techniques were essential (*a*) because of the small scale of the operations, and (*b*) on account of the volatility of the radioactive intermediates and final product.

The reasons for the adoption of the apparatus shown in the diagram are given in the Experimental section where an account is also given of alternative and less satisfactory methods for the small-scale production of phosphorus trichloride.

Experimental.

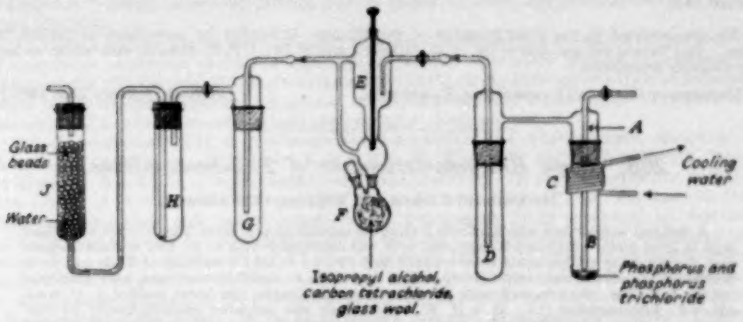
Apparatus.—This is shown in the accompanying diagram. The apparatus was erected in a fume-cupboard equipped with a powerful fan.

(i) The tube *A* was connected to supplies of dry chlorine and dry nitrogen.
(ii) The vessel *B* contained phosphorus and phosphorus trichloride.
(iii) The lower extremity of *A* just touched the top of the P-PCl_3 mixture.
(iv) The coil-condenser *C* was constructed of lead tubing.
(v) *E* was a specially designed graduated collecting vessel. By opening the needle-valve, phosphorus trichloride could be dropped into the reaction flask *F*.
(vi) The trap *G* was cooled in liquid air throughout the experiment. Its purpose was to prevent phosphorus compounds escaping from the apparatus.
(vii) *H* was used to prevent water from *J* being sucked back into *G*.
(viii) Escaping gas was washed free from phosphorus compounds by water contained in *J*.
(ix) All joints were loaded with springs.

Preparation of Phosphorus Trichloride.—The following were placed in the flask *F*: *iso*propyl alcohol (10 ml.), carbon tetrachloride (5 ml.), and a small quantity of glass wool. The taps between *D* and *E* and between *G* and *H* were opened, and *G* and *D* were cooled in liquid air. Radioactive phosphorus (1 g.) was placed in the vessel *B*, and non-radioactive phosphorus trichloride (1 ml.) then added. *B* was then fixed in position and the bottom of the vessel heated by a free flame so that the phosphorus trichloride refluxed gently. A stream of dry chlorine was then slowly admitted through the inlet-tube *A* until nearly all the phosphorus had reacted. If the rate of ingress of the chlorine was too high, the phosphorus began to glow and phosphorus pentachloride was produced. If, on the other hand, the rate was too slow, the reaction-time was unduly long. [If in spite of all precautions a small quantity of phosphorus pentachloride was produced, this tended to block the lower end of the inlet-tube *A*.

By increasing the rate of heating, the more vigorous refluxing would, in general, partly dislodge the solid phosphorus pentachloride and enable the gas to pass through *A*.]

The water passing through the condenser *C* was then cut off, and a stream of nitrogen substituted for the chlorine. This swept the phosphorus trichloride into *D*, where it was trapped. The phosphorus trichloride collected in *D* sometimes contained small quantities of phosphorus and phosphorus pentachloride. These impurities were not, however, carried over in the next stage of the operation, which was to sweep the phosphorus trichloride from *D* into the graduated vessel *E*, the latter being cooled in liquid air while *D* was gently warmed. When the transference was complete, the temperature of *E* was allowed to rise to room temperature and the volume of phosphorus trichloride produced measured on the scale. Yield, *ca.* 90%.



Diisopropyl Fluorophosphonate.—The rod in *E* was raised and the phosphorus trichloride allowed to drop slowly into the flask *F*, which was then detached from the apparatus. The central neck of *F* was fitted to a gas-inlet tube, and a reflux water-condenser attached to the side arm. The top of the condenser was then connected to a gas-washing system similar in construction to *H* and *J*. Nitrogen was passed through the liquid for 2 hours, followed by a stream of chlorine for 25 minutes, *F* being cooled in ice-water while the chlorine was passed. At this stage the liquid was yellowish-green. Nitrogen was again passed through the liquid for 2 hours in order to remove hydrogen chloride and excess of chlorine. The gas-inlet tube was replaced by a mercury-sealed stirrer, and dry sodium fluoride (4·5 g.) was placed in the flask *F*. The mixture was then gently heated under reflux for 5 hours, with vigorous stirring. After cooling, the carbon tetrachloride was removed under reduced pressure and the residual diisopropyl fluorophosphonate distilled: it had b. p. 63—66°/14 mm.

Results.—Phosphorus (1 g.) + phosphorus trichloride (1 ml.) were used. The weight of diisopropyl fluorophosphonate obtained was 5·5 g. (62%). The purity, determined by fluorine analysis on 50 mg. of the active product, was 98·5%.

N.B. In an earlier experiment in which the stirring was omitted, the product contained only 10% of diisopropyl fluorophosphonate.

The radioactive phosphorus used had an activity of 28,000 counts/min./mg. (counter efficiency *ca.* 1%, *i.e.*, specific activity *ca.* 1 mc./g.), whilst the radioactive diisopropyl fluorophosphonate had an activity of 2,200 counts/min./mg. (corrected to zero time). Details of the determination of the purity and of the assessment of the radioactivity will be given in a separate paper.

Precaution against Radiation.—(i) All materials were handled in a fume-cupboard which was provided with stainless-steel trays covered by filter paper. In the event of active material being spilled, the paper could be disposed of and the trays washed.

(ii) Surgical gloves were worn, both to prevent direct contact with active material and to reduce the radiation absorbed by the hands.

(iii) To reduce the radiation a screen of plate glass, lead glass, or "Perspex" was placed in front of the apparatus.

Investigations in Connexion with the Small-scale Preparation of Phosphorus Trichloride.—The standard large-scale preparation of phosphorus trichloride (*Inorg. Synth.*, **2**, 145) utilises a mixture of red phosphorus (200 g.) and phosphorus trichloride (250 ml.) into which chlorine is passed. Even on this scale it is essential to keep the trichloride refluxing, otherwise phosphorus pentachloride is produced. In working out "the one-gram scale" method described above, preliminary experiments were conducted using non-radioactive phosphorus. Some of the more significant observations are recorded below.

(1) In the first experiments, the condenser *C* was not used, as it was expected that the height of the vessel *B* would suffice to prevent the phosphorus trichloride from being swept over into *D*. However, in the absence of a condenser phosphorus trichloride was swept over very rapidly. Even when a condenser was subsequently employed care had to be taken to moderate the gas stream, otherwise some phosphorus trichloride passed into *D*. For this reason, attempts made to prevent the formation of phosphorus pentachloride by diluting the chlorine with nitrogen were abandoned.

(2) If the lower extremity of the tube *A* was placed too high above the surface of the phosphorus–phosphorus trichloride mixture in *B*, excess of chlorine escaped into *D* where it converted the phosphorus trichloride (which had collected) into phosphorus pentachloride. If, on the other hand, the lower extremity of *A* was too low, the orifice almost invariably became blocked with phosphorus penta-

chloride. The best results were obtained when the end of *A* just touched the surface of the reaction mixture.

(3) The effect of variations in the diameter of the lower end of *A* was examined. If this diameter was less than 1 cm., blocking by phosphorus pentachloride was likely. The optimum diameter was 1 cm.

(4) It was supposed that the formation of phosphorus pentachloride would be facilitated by the large size of the bubbles of chlorine. The lower end of *A* was therefore packed with glass wool in an attempt to reduce the bubble size. Although this was in some degree successful, any advantage was outweighed by the fact that the glass wool tended to collect any phosphorus pentachloride formed, and a hard compact mass was formed at the end of *A*. In subsequent experiments the glass wool was not used.

We are indebted to the Chief Scientist of the Ministry of Supply for permission to publish this paper. Our thanks are also due to Dr. A. G. Maddock and to Dr. J. P. E. Human with whom we have had valuable discussions.

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268. *Some Halogeno-derivatives of 2 : 3-Benzacridine.*

By BRIDGET CAIRNS and WILLIAM O. KERMACK.

A method is described which affords 3-chloro-2-naphthoic acid from 3-hydroxy-2-naphthoic acid in good yield. 3-Chloro-2-naphthoic acid was condensed with *o*-, *p*-, and *m*-chloroaniline, and the resulting anilino-acids were cyclized to 5 : 9-, 5 : 7-, and a mixture of 5 : 6- and 5 : 8-*dichloro*-2 : 3-*benzacridine*, respectively. The 5 : 6- and 5 : 8-dichloro-isomers were identified by the fact that, when heated with phosphorus pentachloride, the latter yielded 1 : 5 : 8-*trichloro*-2 : 3-*benzacridine* (IV; R = H, R′ = Cl) which was prepared unambiguously by condensing 1-chloro-2-naphthylamine with 2 : 4-dichlorobenzoic acid and cyclizing the product with phosphorus oxychloride. The orientation of the 5 : 8- and 5 : 6-dichloro-compounds differs from the usual finding that, with such pairs of isomers obtained by the cyclization of 3′-substituted diphenylamine-2-carboxylic acid derivatives, the 5 : 6-isomer has the lower m. p. 7-*Chloro*-2 : 3-*benzacridone* is converted into 1 : 5 : 7-*trichloro*-2 : 3-*benzacridine* (V) by treatment with phosphorus oxychloride containing an excess of phosphorus pentachloride.

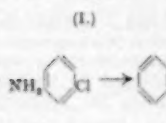
DOBSON, HUTCHISON, and KERMACK (*J.*, 1948, 123) have shown that, whereas derivatives of angular 3 : 4-benzacridine carrying a basic side chain in position 5 and a chlorine atom in position 8 of the acridine nucleus possess appreciable antimalarial activity (*Plasmodium gallinaceum* infections in chicks), the corresponding angular 1 : 2-isomer was completely inactive. Since 8-chloro-5-(dialkylaminoalkylamino)acridines are active, it is clear that a benzene ring fused at the 1 : 2-positions has a strong dystherapeutic effect, while the antimalarial activity persists when a benzene ring is fused at the 3 : 4-positions. A benzene ring at the 2 : 3-positions leads to linear as opposed to angular benzacridine derivatives, and the chemotherapeutic efficiency of this linear type is of evident interest. Bachman and Cowen (*J. Org. Chem.*, 1948, **13**, 89) have prepared 5-chloro-2 : 3-benzacridine (I; R = Cl, X = H) and its 7-methoxy-derivative by cyclizing 3-anilino- and 3-(*p*-anisidino)-2-naphthoic acid with phosphorus oxychloride. They replaced the 5-chlorine atom of these compounds by 6′-methoxy-8′-quinolylamino- and diethylaminopropylamino-side chains and state that the resulting bases are quite inactive. Certain acridine derivatives, though inactive or only slightly active when no chlorine atom (or equivalent atom or group) is present in the molecule, become highly active when a chlorine atom is introduced into position 8 of the acridine nucleus without further alteration of the molecular structure. It was therefore considered desirable to attempt the preparation of derivatives of 2 : 3-benzacridine carrying a basic side chain in position 5 and a chlorine atom in position 8 (or 6, 7, or 9). Preparation of the required intermediates, 5 : 6-, 5 : 7-, 5 : 8-, and 5 : 9-*dichloro*-2 : 3-*benzacridine*, is described in the present paper.

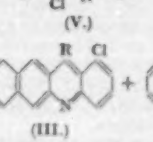
The general scheme followed involved the preparation of 3-(o-*chloroanilino*)-, 3-(m-*chloroanilino*)-, and 3-(p-*chloroanilino*)-2-*naphthoic acid*, and their cyclization with phosphorus oxychloride. Bachman and Cowen (*loc. cit.*) and Albert, Brown, and Duewell (*J.*, 1948, 1284) obtained 3-anilino-2-naphthoic acid in 45% and 10% yield respectively by refluxing a mixture of aniline and 3-hydroxy-2-naphthoic acid, and hydrolysing the resulting 3-anilino-2-naphthanilide with alcoholic potassium hydroxide. When this method was applied to *m*-chloroaniline, much tarring took place, and the reaction mixture set to a solid black mass from which no crystalline product could be isolated on hydrolysis. The synthesis of the required compound was therefore attempted by the Ullmann condensation of 3-chloro-2-naphthoic acid with *m*-chloroaniline.

When 3-hydroxy-2-naphthoic acid was heated with phosphorus pentachloride according to the method recommended by Hosaeus (*Ber.*, **1893**, **26**, 668), much tarring took place and the product, which was very difficult to purify, yielded 3-chloro-2-naphthoic acid in only 25% yield. Strohbach's method (*Ber.*, **1901**, **34**, 4160), in which 3-chloro-2-naphthoyl chloride was distilled under reduced pressure, afforded a very pure product but in very small yield owing to extensive charring. It was eventually found that a 73% yield of 3-chloro-2-naphthoic acid could be obtained by heating a mixture of phosphorus pentachloride and 3-hydroxy-2-naphthoic acid in phosphorus oxychloride as solvent, with a trace of trimethylhexadecylammonium bromide ("Cetavlon") which prevented tarring and so improved the yield considerably (cf. U.S.P. 2,394,279/1946).

3-Chloro-2-naphthoic acid was condensed with *m*-chloroaniline in amyl alcohol in the presence of anhydrous potassium carbonate and copper bronze. The yield of 3-(m-*chloroanilino*)-2-*naphthoic acid* (II) was only 12% but was increased to 72% on the addition of a trace of potassium iodide to the reaction mixture. A similar beneficial effect was found in the analogous condensations of 3-chloro-2-naphthoic acid with *o*- and *p*-chloroaniline.

3-(*o*-*Chloroanilino*)- and 3-(*p*-*chloroanilino*)-2-*naphthoic acid* were cyclized smoothly by phosphorus oxychloride, to yield 5 : 9- (I; R = Cl, X = 9-Cl) and 5 : 7-*dichloro*-2 : 3-*benzacridines* (I; R = Cl, X = 7-Cl), respectively. Cyclization of (II) may afford either 5 : 6-(III; R = Cl) or 5 : 8-*dichloro*-2 : 3-*benzacridine* (IV; R′ = Cl, R = H). A mixture of these dichlorobenzacridines was indeed obtained, the components being separated by fractional crystallisation followed by chromatography on alumina. The problem of the identification of isomers (m. p. 231—232° and 180·5°) then presented itself. In order to obtain a definite derivative of 5 : 8-*dichloro*-2 : 3-*benzacridine*, 1-bromo-2-naphthylamine was condensed with 2 : 4-dichlorobenzoic acid in the presence of anhydrous potassium carbonate, copper bronze, and a trace of potassium iodide. When amyl alcohol was used as solvent, no 4-*chloro*-2-(1-*bromo*-2-*naphthylamino*)*benzoic acid* was isolated; instead, there was obtained a considerable yield of *p*-chlorobenzoic acid, formed evidently by the removal of a chlorine atom from 2 : 4-dichlorobenzoic acid. A similar removal of chlorine from a derivative of *o*-chlorobenzoic acid during


(I.)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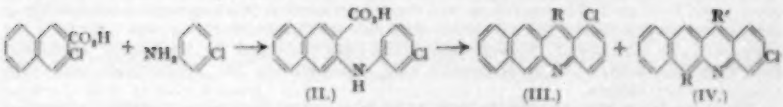
(II.) (III.) (IV.)

an Ullmann condensation has been reported by Goldberg and Kelly (*J.*, **1946**, 102), who isolated *p*-nitrobenzoic acid in experiments with 2-chloro-4-nitrobenzoic acid (cf. Albert and Linnell, *J.*, **1936**, 1614). Bachman and Wetzel (*J. Org. Chem.*, **1946**, **11**, 454), from the product of the condensation of 4-methoxy-1-naphthylamine hydrochloride with 2 : 4-dichlorobenzoic acid, isolated a product, melting range 225—242°, which was soluble in sodium hydrogen carbonate and contained chlorine but no nitrogen; this compound may have been *p*-chlorobenzoic acid (m. p. 241—243°). When, as recommended by Goldberg and Kelly, *iso*propyl alcohol was used in the present experiment, a small quantity of *p*-chlorobenzoic acid was still obtained but some of the desired naphthylaminobenzoic acid was also isolated. The yield however was poor. Bromination of 4-chloro-2-(2-naphthylamino)benzoic acid gave a monobromo-derivative identical with the small quantity of acid obtained by the Ullmann condensation; the bromine atom had thus entered the α-position of the naphthalene nucleus. On cyclization with phosphorus oxychloride the bromo-acid yielded two products—a pale pink compound, m. p. 241—242°, which proved to be the desired 5 : 8-*dichloro*-1-*bromo*-2 : 3-*benzacridine* (IV; R = Br), and a small amount of a dark red crystalline product, m. p. 264—265°, which analysed as, and was later shown to be, 1 : 5 : 8-*trichloro*-2 : 3-*benzacridine* (IV; R = R′ = Cl).

The identity of the latter compound was proved by synthesis: Ullmann condensation of 1-chloro-2-naphthylamine with 2 : 4-dichlorobenzoic acid in *iso*propyl alcohol gave small yields of 4-*chloro*-2-(1-*chloro*-2-*naphthylamino*)*benzoic acid* and *p*-chlorobenzoic acid, and the former

product was cyclized to the 1 : 5 : 8-trichloro-compound described above. The identification of this compound demonstrated that during the treatment with phosphorus oxychloride replacement of the bromine by chlorine must have occurred, this being perhaps analogous to the formation of 5-chloro-6-aminoquinoline from 5-bromo-6-aminoquinoline when the latter is heated in a sealed tube with concentrated hydrochloric acid (Kern, Diss., Freiberg, 1907, 7).

In order to utilize 5 : 8-dichloro-1-bromo-2 : 3-benzacridine for the identification of the dichloro-2 : 3-benzacridines, attempts were made to remove the bromine atom. The compound was treated with reducing agents, such as stannous chloride and concentrated hydrochloric acid, and phosphorus and hydriodic acid. The former reagent merely hydrolysed it to the corresponding *8-chloro-1-bromo-2 : 3-benzacridone*, and the latter yielded a compound which may have been 8-chloro-1-bromo-2 : 3-benzacridine. In view of the ready removal of bromine from such compounds as 1-bromo-2-naphthylamine (in the presence of acid reducing agents) this difficulty in removing the bromine atom is somewhat surprising. Attempts to introduce bromine into the chloroacridones obtained from 5 : 6- and 5 : 8-dichlorobenzacridine, in the hope that the bromine would enter position 1, were unsuccessful. However, on treating the dichloro-compounds with a suitable proportion of phosphorus pentachloride, chlorination took place. The isomer, m. p. 180·5°, yielded 1 : 5 : 8-trichloro-2 : 3-benzacridine and so was 5 : 6-dichloro-2 : 3-benzacridine. The isomer, m. p. 131—132°, yielded no trichloro-derivative, but various crystalline compounds were isolated which gave analytical data suggesting the presence of five chlorine atoms in the molecule; it was concluded that this was the 5 : 6-dichloro-isomer.

Lehmstedt and Schrader (*Ber.*, 1937, **70**, 838) obtained mixtures of 6- and 8-substituted 5-chloroacridines by the cyclization of 3'-substituted diphenylamine-2-carboxylic acids with phosphorus oxychloride. In every case the compound with the lower melting point proved to be the 6-substituted 5-chloro-isomer and that with the higher melting point the 8-substituted 5-chloro-isomer. Similar results have been quoted by Bradbury and Linnell (*J.*, 1942, 377) and it seemed as if the principle held that the 5 : 8-isomer had always a higher melting point than the 5 : 6-isomer. However, Dauben (*J. Amer. Chem. Soc.*, 1948, **70**, 2420) on cyclizing 2-(*m*-chloroanilino)-5-methoxybenzoic acid with phosphorus oxychloride isolated a pure compound, m. p. 182°, which was evidently the 5 : 6-dichloro-isomer, as 5 : 8-dichloro-3-methoxyacridine (m. p. 162°) is a well-known compound prepared by Mauss and Mietzach during the synthesis of mepacrine. From this and the present case, it is clear that the above-mentioned generalisation is not of universal validity.

A chlorination process similar to that described for 5 : 6- and 5 : 8-dichlorobenzacridine took place when 7-chloro-2 : 3-benzacridone was treated with excess of phosphorus pentachloride in phosphorus oxychloride. The resultant dark-red trichlorobenzacridine was probably, by analogy, *1 : 5 : 7-trichloro-2 : 3-benzacridine*. This was confirmed by condensing 1-chloro-2-naphthylamine with 2 : 5-dichlorobenzoic acid and cyclizing the intermediate acid with phosphorus oxychloride.

When heated with acid, the 5-chloro-2 : 3-benzacridine derivatives described above are readily converted into the corresponding acridones, the melting points of which are above 300°, except that of *9-chloro-2 : 3-benzacridone* (m. p. 271—272°). These chloro-acridines and -acridones give characteristic colours with concentrated sulphuric acid (see Table); it will be

2 : 3-Benzacridine.	Colour in H_2SO_4.	2 : 3-Benzacridone.	Colour in H_2SO_4.
5 : 6-Dichloro-	Purple	6-Chloro-	Red
5 : 7- ,,	,,	7- ,,	,,
5 : 8- ,,	,,	8- ,,	,,
5 : 9- ,,	,,	9- ,,	,,
1 : 5 : 8-Trichloro-	Blue	1 : 8-Dichloro-	Purple
1 : 5 : 7- ,,	,,	8-Chloro-1-bromo-	Pale yellow
5 : 8-Dichloro-1-bromo-	Pale yellow		

observed that 5 : 8-dichloro-1-bromo-2 : 3-benzacridine and the corresponding acridone give only a yellowish colour whereas the other compounds give purple, blue, or red solutions. The bromo-derivative also differs from its chloro-analogues in that it gives no fluorescence in benzene, whereas the others give solutions with a brilliant green fluorescence.

Experimental.

3-Chloro-2-naphthoic Acid.—Dried 3-hydroxy-2-naphthoic acid (30 g.) was slowly stirred into a mixture of phosphorus pentachloride (100 g.), phosphorus oxychloride (50 c.c.), and a trace of "Cetavlon." The reaction was exothermic. The mixture was heated under reflux for 6 hours in an

oil-bath at 160—170°, the phosphorus oxychloride removed by distillation, and the dark brown oily residue poured into water. The mixture was warmed slightly on the steam-bath to hydrolyse the acid chloride, 3-chloro-2-naphthoic acid being formed as a pale yellow solid, which was filtered off, purified by extraction with aqueous ammonia and reprecipitation with hydrochloric acid, and recrystallised from aqueous alcohol as pale yellow needles, m. p. 210° (26·5 g.).

3-(*o-Chloroanilino*)-2-*naphthoic Acid.*—A mixture of 3-chloro-2-naphthoic acid (5 g.), *o*-chloroaniline (3·25 g.), anhydrous potassium carbonate (3·75 g.), copper bronze (0·15 g.), potassium iodide (0·05 g.), and amyl alcohol (40 c.c.) was heated under reflux for 6 hours in an oil-bath at 150°. The solution became very dark and on cooling deposited a small amount of solid which was filtered off, washed thoroughly with acetone, and extracted with 2*N*-sodium carbonate. The extract on acidification with hydrochloric acid yielded a small amount of yellow 3-hydroxy-2-naphthoic acid which on recrystallisation from aqueous alcohol melted at 220°. The amyl-alcoholic filtrate and acetone washings were steam-distilled, and the residual black oil was thoroughly extracted with hot potassium carbonate solution. On acidification of the hot extract with glacial acetic acid, a canary-yellow solid separated. This was filtered off, and the filtrate acidified with hydrochloric acid. A small quantity of pale yellow 3-chloro-2-naphthoic acid was precipitated which crystallised from aqueous alcohol as needles, m. p. 210°. The canary-yellow 3-(*o-chloroanilino*)-2-*naphthoic acid* after several crystallisations from alcohol melted at 228—230° (4·5 g.) (Found : C, 68·2; H, 4·0; N, 4·85. $C_{17}H_{12}O_2NCl$ requires C, 68·6; H, 4·05; N, 4·75%).

3-(*p-Chloroanilino*)-2-*naphthoic Acid.*—A mixture of 3-chloro-2-naphthoic acid (5 g.), *p*-chloroaniline (3·25 g.), anhydrous potassium carbonate (3·75 g.), copper bronze (0·15 g.), potassium iodide (0·05 g.), and amyl alcohol (40 c.c.) similarly gave 3-(*p-chloroanilino*)-2-*naphthoic acid* as a bright yellow solid which crystallised from benzene as needles, m. p. 245° (4·5 g.) (Found : C, 68·2; H, 4·5; N, 4·6%).

3-(*m-Chloroanilino*)-2-*naphthoic Acid.*—This *acid*, prepared as in the previous case, but from *m*-chloroaniline, was obtained as a canary-yellow solid which crystallised from alcohol as needles, m. p. 227—229° (Found : C, 67·5; H, 4·3; N, 4·4. $C_{17}H_{12}O_2NCl,\frac{1}{4}C_2H_5O$ requires C, 67·5; H, 4·7; N, 4·4%).

5 : 9-*Dichloro*-2 : 3-*benzacridine.*—A mixture of 3-(*o*-chloroanilino)-2-naphthoic acid (6 g.) and phosphorus oxychloride (60 c.c.) was heated under reflux in an oil-bath at 150° for 2 hours. The solution became dark purple, and after removal of the oxychloride, the dark purple, oily residue was poured into a mixture of ice, chloroform, and concentrated ammonia solution. The orange chloroform layer, which exhibited a green fluorescence, was washed, dried (Na_2SO_4), and freed from solvent. The orange-red solid residue, after crystallising from dry benzene, yielded 5 : 9-*dichloro*-2 : 3-*benzacridine* as rods, m. p. 203° (4 g.) (Found : C, 66·7; H, 2·8; N, 5·0. $C_{17}H_9NCl_2,\frac{1}{4}H_2O$ requires C, 66·45; H, 3·2; N, 4·6%).

9-*Chloro*-2 : 3-*benzacridone.*—5 : 9-Dichloro-2 : 3-benzacridine was heated on the steam-bath with 3*N*-hydrochloric acid for ½ hour. The reddish colour of the acridine changed to the orange-yellow of the acridone. The latter was filtered off, washed, and crystallised, first from alcohol and then from benzene, as yellow crystals, m. p. 271—272° (Found : C, 72·2; H, 3·6; N, 4·8. $C_{17}H_{10}ONCl$ requires C, 73·0; H, 3·6; N, 5·0%).

5 : 7-*Dichloro*-2 : 3-*benzacridine.*—3-(*p*-Chloroanilino)-2-naphthoic acid (5 g.) and phosphorus oxychloride similarly gave 5 : 7-*dichloro*-2 : 3-*benzacridine* as an orange solid which after several crystallisations from benzene melted at 227—228° (3·5 g.). When this compound was dried for 6 hours *in vacuo* at 70° over phosphoric oxide, the melting point rose to 239—240° (decomp.) (Found : C, 68·95; H, 2·9; N, 4·8. $C_{17}H_9NCl_2$ requires C, 68·45; H, 3·0; N, 4·7%).

7-*Chloro*-2 : 3-*benzacridone.*—5 : 7-Dichloro-2 : 3-benzacridine was heated on the steam-bath for ½ hour with 2*N*-hydrochloric acid. The resulting 7-*chloro*-2 : 3-*benzacridone* was filtered off, washed with water, and recrystallised from alcohol, in which it dissolved giving a yellow solution with a brilliant green fluorescence. It had m. p. >360° (Found: C, 70·5; H, 3·4; N, 4·3. $C_{17}H_{10}ONCl,\frac{1}{4}H_2O$ requires C, 70·7; H, 3·8; N, 4·8%).

Action of Phosphorus Pentachloride on 7-*Chloro*-2 : 3-*benzacridone.*—A mixture of 7-chloro-2 : 3-benzacridone, phosphorus oxychloride, and excess of phosphorus pentachloride was heated under reflux at 150° for 2 hours and the dark-red product worked up as described previously. 1 : 5 : 7-*Trichloro*-2 : 3-*benzacridine* was isolated as a dark red solid which crystallised from light petroleum (b. p. 60—80°) as needles m. p. 265—266° (Found : C, 61·4; H, 2·3; N, 4·2. $C_{17}H_9NCl_3$ requires C, 61·35; H, 2·4; N, 4·2%).

5-*Chloro*-2-(1-*chloro*-2-*naphthylamino*)*benzoic Acid.*—A mixture of 1-chloro-2-naphthylamine (2·5 g.), 2 : 5-dichlorobenzoic acid (2·7 g.), anhydrous potassium carbonate (2 g.), *iso*propyl alcohol (30 c.c.), copper bronze (0·1 g.), and a trace of potassium iodide was heated under reflux at 150° for 6 hours. The greenish solution was then filtered, the *iso*propyl alcohol removed by steam-distillation, and the residual oil extracted with dilute aqueous ammonia. On acidification of the extract with glacial acetic acid, a greenish-yellow precipitate was obtained, which after crystallisation from benzene yielded 5-*chloro*-2-(1-*chloro*-2-*naphthylamino*)*benzoic acid*, as yellow needles, m. p. 266—267° (1·2 g.) (Found : C, 61·35; H, 3·2. $C_{17}H_{11}O_2NCl_2$ requires C, 61·45, H, 3·3%).

1 : 5 : 7-*Trichloro*-2 : 3-*benzacridine.*—A mixture of 5-chloro-2-(1-chloro-2-naphthylamino)benzoic acid (1 g.) and phosphorus oxychloride (10 c.c.) was heated under reflux at 150° for 2 hours and the dark-red product worked up as described previously. 1 : 5 : 7-Trichloro-2 : 3-benzacridine (cf. above) crystallised from light petroleum (b. p. 60—80°) as dark red needles, m. p. 265—266° (Found : C, 61·2; H, 2·4; N, 4·2%).

5 : 6- *and* 5 : 8-*Dichloro*-2 : 3-*benzacridine.*—3-(*m*-Chloroanilino)-2-naphthoic acid (4 g.) and phosphorus oxychloride (40 c.c.) were heated under reflux at 180° for 2 hours. After removal of the excess of phosphorus oxychloride the dark-purple oily residue was poured into a mixture of ice, chloroform, and concentrated aqueous ammonia. The orange chloroform layer, which exhibited a green fluorescence, was washed with water and dried (Na_2SO_4), and the solvent removed. The reddish-orange solid (3·5 g.) which remained was fractionally crystallised from dry benzene, to give (i) light orange needles, m. p. 210—220°, (ii) deep-orange crystals, m. p. 190—200°, (iii) orange-red crystals, m. p. 150—165°, and (iv) a dark-brown amorphous mass. Fraction (i), after several crystallisations from

light petroleum (b. p. 60—80°), gave 5 : 6-*dichloro*-2 : 3-*benzacridine* as long, pale orange needles, m. p. 231—232° (decomp.) (3·5 g.) (Found : C, 68·5; H, 3·1; N, 4·8. $C_{17}H_9NCl_2$ requires C, 68·4; H, 3·0; N, 4·7%). The remaining material was dissolved in 1 : 1 benzene–light petroleum (b. p. 60—80°) and chromatographed on alumina. A light orange band passed quickly down the column and was collected as an orange solution with a green fluorescence. On reducing the volume of this solution a further quantity of 5 : 6-dichloro-2 : 3-benzacridine, m. p. 231—232° crystallised. A reddish-orange band was strongly adsorbed at the top of the column. When the light-orange band had been completely washed through, the column was extruded and extracted with hot benzene. The solvent was then removed and the resulting 5 : 8-*dichloro*-2 : 3-*benzacridine* crystallised from light petroleum (b. p. 60—80°) as reddish-orange needles, m. p. 180·5° (Found : C, 68·4; H, 3·2; N, 4·8. $C_{17}H_9NCl_2$ requires C, 68·4; H, 3·0; N, 4·7%).

6-*Chloro*-2 : 3-*benzacridone*.—5 : 6-Dichloro-2 : 3-benzacridine was heated on the steam-bath with 2*N*-hydrochloric acid for ½ hour. The resulting yellowish-orange 6-*chloro*-2 : 3-*benzacridone*, crystallised several times from alcohol in which it gave a bright-green fluorescence, had m. p. > 360° (Found : C, 72·5; H, 3·5. $C_{17}H_{10}ONCl$ requires C, 73·0; H, 3·6%).

8-*Chloro*-2 : 3-*benzacridone*.—5 : 8-Dichloro-2 : 3-benzacridine similarly gave 8-*chloro*-2 : 3-*benzacridone* as an orange solid which, crystallised from alcohol, had m. p. 360° (Found : N, 4·7. $C_{17}H_{10}ONCl$ requires N, 5·0%).

4-*Chloro*-2-(2-*naphthylamino*)*benzoic Acid* (Dobson, Hutchison, and Kermack, *J.*, 1948, 123).—β-Naphthylamine (5·7 g.), potassium 2 : 4-dichlorobenzoate (9·2 g.), amyl alcohol (30 c.c.), copper bronze (0·1 g.), and potassium iodide (0·05 g.) were heated under reflux at 150° for 6 hours. On cooling, the dark purple oily solid which separated was filtered off and washed thoroughly with acetone; all the purple material dissolved, leaving behind a small amount of greenish-white solid, which on purification was identified as *p*-chlorobenzoic acid, m. p. 240°. The amyl-alcoholic filtrate and the acetone washings were steam-distilled, and the black tarry residue thoroughly extracted with dilute aqueous ammonia. (Extraction of the considerable residue with dilute hydrochloric acid yielded β-naphthylamine, m. p. 112°.) The hot ammoniacal extract was acidified with acetic acid, a purplish solid being precipitated. Treated with charcoal in aqueous alcohol solution and further crystallised from benzene, this gave 4-chloro-2-(2-naphthylamino)benzoic acid as pale yellow needles, m. p. 231—232° (9·5 g.).

4-*Chloro*-2-(1-*bromo*-2-*naphthylamino*)*benzoic Acid*.—(*a*) 1-Bromo-2-naphthylamine (6·6 g.), 2 : 4-dichlorobenzoic acid (5·7 g.), anhydrous potassium carbonate (4·06 g.), copper bronze (0·1 g.), potassium iodide (0·5 g.), and *iso*propyl alcohol (50 c.c.) were heated under reflux for 6 hours at 150°. On cooling, the greenish solid was filtered off, washed with acetone and extracted with 2*N*-sodium carbonate, which removed *p*-chlorobenzoic acid, m. p. 241—243°. Steam-distillation of the *iso*propyl-alcoholic filtrate left a black oily residue which was thoroughly extracted with potassium carbonate. Acidification of the extract, with acetic acid, afforded a purplish solid (0·5 g.), which was recrystallised several times from aqueous alcohol and benzene and finally yielded 4-*chloro*-2-(1-*bromo*-2-*naphthylamino*)*benzoic acid* as pale yellow rectangular plates, which softened at 262° and melted at 272° (0·2 g.) (Found : C, 54·3; H, 3·0; N, 3·6. $C_{17}H_{11}O_2NClBr$ requires C, 54·2; H, 2·9; N, 3·7%).

(*b*) 4-Chloro-(2-naphthylamino)benzoic acid (10 g.) was dissolved in cold glacial acetic acid, and bromine (5·35 g.) in the same solvent was slowly stirred in. After a few minutes a pale yellow solid separated, and after ½ hour was filtered off, washed, and crystallised several times from alcohol, giving pale yellow rectangular plates which softened at 262° and melted at 272°. A mixed m. p. with the acid prepared in (*a*) was not depressed.

4-*Chloro*-2-(1-*chloro*-2-*naphthylamino*)*benzoic Acid*.—1-Chloro-2-naphthylamine (5 g.), 2 : 4-dichlorobenzoic acid (5·4 g.), anhydrous potassium carbonate (3·88 g.), copper bronze (0·1 g.), potassium iodide (0·05 g.), and *iso*propyl alcohol (50 c.c.) were heated under reflux for 6 hours at 150°. The solution became greenish-blue, and on cooling, the greenish-white solid which separated was filtered off, washed with acetone, and extracted with hot dilute aqueous ammonia, which removed *p*-chlorobenzoic acid, m. p. 241—243°. The *iso*propyl-alcoholic filtrate and acetone washings were steam-distilled. A white solid, m. p. 56°, which solidified in the condenser was identified as unchanged 1-chloro-2-naphthylamine. The black oily residue was first extracted with dilute hydrochloric acid, which removed unchanged 1-chloro-2-naphthylamine, m. p. 56°. The oily material, insoluble in dilute hydrochloric acid, was extracted with dilute aqueous ammonia. Most of it dissolved, leaving only a small amount of black oil. On acidification of the hot extract with acetic acid, a yellow solid separated. (The filtrate on addition of hydrochloric acid yielded a further quantity of *p*-chlorobenzoic acid.) The yellow solid—4-*chloro*-2-(1-*chloro*-2-*naphthylamino*)*benzoic acid*—crystallised from aqueous alcohol as rectangular tetrahedra, and from benzene as long needles, which softened at 230° and melted at 255°. After drying at 80° over phosphoric oxide for 3 hours this compound, melted from 235° to 245° (Found : C, 61·5; H, 3·25; N, 4·4. $C_{17}H_{11}O_2NCl_2$ requires C, 61·45; H, 3·3; N, 4·2%).

1 : 5 : 8-*Trichloro*-2 : 3-*benzacridine*.—4-Chloro-2-(1-chloro-2-naphthylamino)benzoic acid (1 g.) and phosphorus oxychloride (10 c.c.) were heated under reflux for 2 hours at 150°. The solution became deep red and finally purplish-brown. On removal of the excess of oxychloride, and pouring of the residue into a mixture of ice, chloroform, and concentrated aqueous ammonia, the chloroform layer became deep red and an orange-green fluorescence was observed. This layer was washed with water and dried (Na_2SO_4), and the chloroform removed. A deep-red solid was obtained which after 4 crystallisations from benzene and light petroleum (b. p. 60—80°) melted from 190° to 230°. It was dissolved in 1 : 1 benzene–light petroleum (b. p. 60—80°) and chromatographed on alumina. A deep-red band passed quickly down the column, leaving a yellow band strongly adsorbed on the alumina. The red-band was collected as a yellow-orange fluorescent solution, from which, on concentration, a deep-red solid crystallised having m. p. 257—259°. Recrystallisation from light petroleum yielded 1 : 5 : 8-*trichloro*-2 : 3-*benzacridine* as long red rods m. p. 262—263° (0·6 g.) (Found : C, 61·05; H, 2·45; N, 4·4. $C_{17}H_8NCl_3$ requires C, 61·35; H, 2·4; N, 4·2%). The yellow band which was more strongly adsorbed on the column was washed through with benzene and collected as a yellow, non-fluorescent solution. On concentration a very small quantity of an orange-pink solid crystallised which after recrystallisation

from light petroleum (b. p. 40—60°) melted at 238° (Found : C, 59·7; H, 2·3%). The analytical figures suggest that this material is an isomeric trichlorobenzacridine. It may have been formed from a trace of an isomer present in the original 1-chloro-2-naphthylamine.

1 : 8-*Dichloro*-2 : 3-*benzacridone*.—1 : 5 : 8-Trichloro-2 : 3-benzacridine was heated on the steam-bath with 2N-hydrochloric acid for ½ hour. A yellow solid was formed which dissolved in hot alcohol, giving a yellow solution with a brilliant green fluorescence. On cooling 1 : 8-*dichloro*-2 : 3-*benzacridone* separated as yellow needles which, after several recrystallisations from alcohol, melted at 349—350° (Found : C, 64·55; H, 2·6; N, 4·3. $C_{17}H_9ONCl_2$ requires C, 64·95; H, 2·85; N, 4·5%).

5 : 8-*Dichloro*-1-*bromo*-2 : 3-*benzacridine*.—4-Chloro-2-(1-bromo-2-naphthylamino)benzoic acid (2 g.) and phosphorus oxychloride (20 c.c.) were heated under reflux at 150° for 2 hours. The solution became dark-purple and, on cooling, green. Treated as recorded previously, this gave a scarlet fluorescent chloroform layer and thence a scarlet solid, which was triturated with small amounts of cold benzene. Most of the deep-red material dissolved, leaving a pale pink residue. This residue was dissolved in benzene, and the solution was heated with charcoal and reduced in volume; 5 : 8-*dichloro*-1-*bromo*-2 : 3-*benzacridine* crystallised as a pale pink solid which after several recrystallisations from benzene–ether melted at 241—242° (1·2 g.) (Found : C, 54·3; H, 1·9; N, 3·4. $C_{17}H_8NCl_2Br$ requires C, 54·1; H, 2·1; N, 3·7%). On evaporation of the dark red benzene solution, a small quantity of a dark red solid was obtained having m. p. 170—190°. This was dissolved in 1 : 1 benzene–light petroleum and chromatographed on alumina. A red band passed quickly down the column and was collected as a yellowish-orange solution with a green fluorescence; on concentration, deep-red, rod-shaped crystals separated, which after several crystallisations from light petroleum (b. p. 40—60°) melted at 264—265° (Found : N, 4·3. $C_{17}H_8NCl_3$ requires N, 4·2%). This compound did not depress the m. p. of authentic 1 : 5 : 8-trichloro-2 : 3-benzacridine m. p. 263—264°, described above.

8-*Chloro*-1-*bromo*-2 : 3-*benzacridone*.—5 : 8-Dichloro-1-bromo-2 : 3-benzacridine was heated on the steam-bath with 2N-hydrochloric acid for ½ hour. The buff-coloured solid which formed was filtered off, washed, and dissolved in hot alcohol, giving a yellow solution with only a faint green fluorescence. On cooling, 8-*chloro*-1-*bromo*-2 : 3-*benzacridone* crystallised as buff-coloured needles, m. p. > 360° (Found : C, 56·6; H, 2·6; N, 4·2; $C_{17}H_{10}ONClBr$ requires C, 56·9; H, 2·5; N, 3·9%).

8-*Chloro*-1-*bromo*-2 : 3-*benzacridine*.—8-Chloro-1-bromo-2 : 3-benzacridone (0·5 g.), red phosphorus (1 g.), and hydriodic acid (10 c.c.) were heated on the water-bath for 3 hours and then poured into water. The dark-red solid was filtered off, washed with water, and extracted with alcohol; concentration gave an orange solid which was extracted with acetone; this solution was treated with charcoal and then reduced in volume. A pale yellow solid, probably 8-*chloro*-1-*bromo*-2 : 3-*benzacridine*, separated which after several crystallisations from acetone melted at 212—213° (Found : C, 58·8; N, 2·6; $C_{17}H_9NClBr$ requires C, 59·6; N, 2·6%). This compound in contrast to the original acridone, is readily soluble in organic solvents and in dilute acids.

Action of Phosphorus Pentachloride on 5 : 8-*Dichloro*-2 : 3-*benzacridine*.—(*a*) 5 : 8-Dichloro-2 : 3-benzacridine (0·5 g.), phosphorus pentachloride (0·7 g., 2 moles), and phosphorus oxychloride (5 c.c.) were heated under reflux for 2 hours at 150°, and treated as usual. The rose-red solid residue (m. p. 240—244°) from the chloroform was dissolved in light petroleum (b. p. 60—80°) and chromatographed on alumina. A red band passed quickly through the column. Six 100-c.c. fractions—orange fluorescent solutions—were collected and reduced in volume. The first two fractions yielded deep-red, rod-shaped crystals which after several recrystallisations from the same solvent melted at 262—263° (Found : C, 60·9; H, 2·8. Calc. for $C_{17}H_9NCl_2$: C, 61·35; H, 2·4%). This compound did not depress the m. p. of authentic 1 : 5 : 8-trichloro-2 : 3-benzacridine. The next four fractions from the chromatogram also yielded red solids, lighter in colour than the 1 : 5 : 8-trichloro-compound and melting over the range 200° to 240°. No purification was effected by crystallisation.

(*b*) The experiment was repeated using three moles of phosphorus pentachloride, and the product worked up as in previous experiments. The chloroform became only faintly coloured and on removal of the solvent a pink solid was obtained, which after trituration with cold benzene and recrystallisation from light petroleum (b. p. 60—80°) was obtained as pale pink needles which melted to a deep-red liquid at 205°. This material gave analytical data suggesting its formulation as a *perchloride* of a trichlorobenzacridine (Found : C, 50·05; H, 2·0; N, 3·2. $C_{17}H_9NCl_4$ requires C, 50·55; H, 2·0; N, 3·5%).

Action of Phosphorus Pentachloride on 5 : 6-*Dichloro*-2 : 3-*benzacridine*.—Three experiments were carried out with 5 : 6-dichloro-2 : 3-benzacridine, similar to those described above, using 1, 2, and 3 moles of phosphorus pentachloride, respectively. In the first, no reaction took place, and the original dichloroacridine was recovered. With 2 moles, a pale pink solid was obtained which after several crystallisations from light petroleum yielded pale pink rectangular tetrahedra which became deep red at 175—180° and melted sharply at 183° (Found : C, 50·15; H, 2·1. $C_{17}H_9NCl_4$ requires C, 50·55; H, 2·0%). The analytical data suggest that this compound may also be a *perchloride* of a trichlorobenzacridine. With 3 moles of phosphorus pentachloride the only pure product isolated was a small amount of a dark red solid, m. p. 185°, insufficient for analysis.

We are indebted to the Carnegie Trust for the Universities of Scotland for the award of a scholarship to one of us (B. C.), and to the M.R.C. for a grant which has defrayed part of the expenses.

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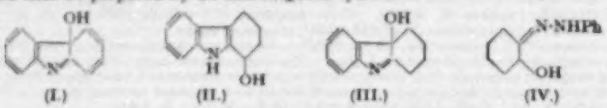
269. *The Formation of Osazones. Part I. The Reaction of 2-Hydroxycyclohexanone with Arylhydrazines.*

By G. J. Bloink and K. H. Pausacker.

The reaction between 2-hydroxy*cyclo*hexanone and various arylhydrazines has been studied. In aqueous-alcoholic sulphuric acid, the corresponding 1-ketotetrahydrocarbazole only is formed, whereas in alcohol alone (with phenylhydrazine) a mixture of 1-ketotetrahydrocarbazole and the bisphenylhydrazone of *cyclo*hexane-1 : 2-dione was obtained. In glacial acetic acid, osazone formation only occurred, except that when *p*-methoxyphenylhydrazine was used, the 1-ketotetrahydrocarbazole was alone formed.

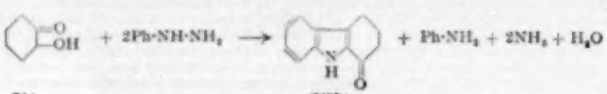
In order to prepare the compound formulated as 11-hydroxy-11-*iso*carbazole (I) by Barnes, Pausacker, and Schubert (*J.*, 1949, 1381), it was decided to proceed as follows. Cyclisation of the phenylhydrazone of 2-hydroxy*cyclo*hexanone should yield a mixture of the neutral 1-hydroxy-1 : 2 : 3 : 4-tetrahydrocarbazole (II) and the basic 11-hydroxy-1 : 2 : 3 : 4-tetrahydro-11-*iso*carbazole (III). Dehydrogenation of the latter product should then yield (I), which would thus be prepared by an unambiguous synthesis.



(I.) (II.) (III.) (IV.)

Bergmann and Gierth (*Annalen*, 1926, **448**, 72) described the preparation of the phenylhydrazone (IV) (m. p. 121°) of 2-hydroxy*cyclo*hexanone by condensation of phenylhydrazine with 2-hydroxy*cyclo*hexanone (V) in aqueous acetic acid. Attempts to repeat this work proved abortive, the only pure product isolated being the bisphenylhydrazone (VI) of *cyclo*hexane-1 : 2-dione (an osazone) (m. p. 153°). However, when equimolecular amounts of phenylhydrazine and (V) were heated, in a boiling water-bath, under reduced pressure, a loss in weight corresponding to one mole of water was noted. The resulting red, viscous oil did not contain any (VI) and could not be induced to crystallise. This oil was then heated with aqueous-alcoholic sulphuric acid, but neither (II) nor (III) was isolated. Instead, the neutral fraction yielded 1-ketotetrahydrocarbazole (VII), and the basic fraction was identified as aniline. (VII) was found to be identical (mixed m. p.) with the product obtained from the cyclisation of the monophenylhydrazone of *cyclo*hexane-1 : 2-dione (Coffey, *Rec. Trav. chim.*, 1923, **42**, 528). Similar results were obtained when the reagents were heated with aqueous-alcoholic sulphuric acid without prior condensation.

It thus seems probable that, in these reactions in sulphuric acid, phenylhydrazine is acting as an oxidising agent, as in the preparation of osazones. This hypothesis was verified by the observation that the yield of (VII) was doubled when two moles of phenylhydrazine were heated with one mole of (V) in aqueous-alcoholic sulphuric acid under the same conditions, thus :

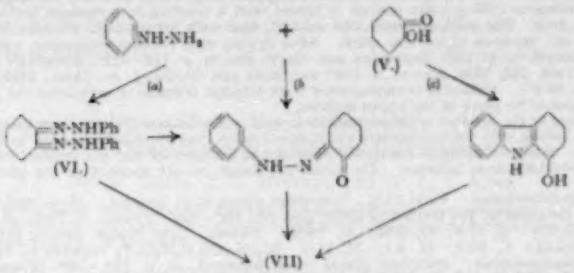


(V.) (VII.)

As far as the authors are aware, this is the first recorded example of the simultaneous oxidation and cyclisation of an α-hydroxy-ketone. It is therefore of interest to determine the course of the reaction.

It is unlikely that the reaction would follow course (a) for, as Semple (*J. Amer. Chem. Soc.*, 1934, **56**, 1352) has pointed out, osazone formation (for glucose) is inhibited in the presence of dilute mineral acid, although hydrazone formation can take place. In order to verify that the osazone (VI) is not involved as an intermediate in the reaction, (VI) was treated under the same conditions. A surprising result was obtained, namely, a 21% conversion of (VI) into (VII). It is still considered that (VI) is not an intermediate, however, for a much greater yield (46%) of (VII) was obtained by starting with phenylhydrazine and (V). It is nevertheless interesting that (VI) may be converted into (VII), as osazones are generally resistant to cyclisation. This ready ring closure may be correlated with the ready formation of tetrahydrocarbazoles by the Fischer method. It thus appears that the reaction follows either

course (*b*) or course (*c*), and at present no distinction can be made between these two possibilities except to say that mechanism (*b*) is perhaps more analogous to osazone formation. It should also be noted that both these reactions imply a direct oxidation of ·CH·OH· to ·CO·. Similar reactions were noted when *p*-tolyl-, *p*-methoxyphenyl-, and *p*-ethoxyphenylhydrazine were used in place of phenylhydrazine.



When a mixture of phenylhydrazine and (V) was refluxed, in ethyl-alcoholic solution, without an acid catalyst, a copious evolution of ammonia took place and both (VI) and (VII) were isolated from the reaction mixture. This shows that osazone formation can take place in an alkaline medium and provides an example of the Fischer indole synthesis occurring without the addition of an acid catalyst.

Finally, the condensation of phenylhydrazine and (V) in glacial acetic acid at 0° resulted in rapid formation of (VI) (cf. Bergmann and Gierth, *loc. cit.*), the product being precipitated almost quantitatively. (VII) could not be isolated from the reaction mixture. With three moles of various substituted phenylhydrazine per mole of (V) in glacial acetic acid at 0°, the yields of osazone, after one hour, were 88, 72, 70, 16, and 0% when the substituents were *p*-nitro, *p*-chloro, unsubstituted, *p*-methyl, and *p*-methoxy, respectively. As all these osazones were sparingly soluble in glacial acetic acid, the yields probably give an approximate measure of the relative reaction rates. It is thus seen that osazone formation takes place most readily when the substituent has an overall effect ($-I$ or $-T$) and occurs very slowly indeed when *p*-methyl ($+I$) is the substituent and not at all when the substituent is *p*-methoxy ($+T > -I$). When the various hydrazines were set aside for a long time with (V) in glacial acetic acid it was found that, except when *p*-methoxyphenylhydrazine was used, the corresponding osazone was the only product isolated even though the sparing solubility of the osazones in most solvents allows their ready separation from any 1-ketotetrahydrocarbazole formed simultaneously. When *p*-methoxyphenylhydrazine was used, however, it was impossible to isolate any osazone, but instead an 89% yield of 1-*keto*-6-*methoxyltetrahydrocarbazole* was obtained.

It is thus seen that in glacial acetic acid both tetrahydrocarbazole and osazone formation are possible. When *p*-nitro-, *p*-chloro-, unsubstituted, and *p*-methyl-phenylhydrazines were used, the rate of osazone formation decreased in this order but must be much greater than the rate of tetrahydrocarbazole formation. This inference is in accord with the statement of Pigman and Geopp ("Chemistry of the Carbohydrates," Academic Press, 1948, p. 404) that "osazone formation is favoured by the presence of electron-attracting groups attached to the hydrazine radical." However, when *p*-methoxyphenylhydrazine was used, the rate of tetrahydrocarbazole formation must have been much greater than that of osazone formation. This result is in accord with the above statement, and in addition we have recently found (unpublished results) that the *p*-methoxyphenylhydrazone of *cyclo*hexanone is converted into the corresponding tetrahydrocarbazole (in glacial acetic acid) much more rapidly than the *p*-nitro-, unsubstituted, or *p*-methyl-phenylhydrazones of *cyclo*hexanone (in that order).

It is interesting that, when Adkins and Rossow (*J. Amer. Chem. Soc.*, 1949, **71**, 3836) treated 2-methoxy*cyclo*hexanone with 2 : 4-dinitrophenylhydrazine in the presence of alcoholic hydrochloric acid, the corresponding osazone was the only product isolated. Although our results indicate that mineral acid should favour the formation of a 1-ketotetrahydrocarbazole, it is well known that dinitrophenylhydrazones are particularly resistant to Fischer cyclisation, and so the alternative osazone formation, favoured by the presence of nitro-groups, takes place after hydrolysis of the methoxyl group.

Finally, it may be noted that 2-chlorocyclohexanone also condenses with phenylhydrazine in glacial acetic acid to form (VI).

A kinetic investigation of osazone formation is now proceeding.

Experimental.

2-Hydroxycyclohexanone (V).—The method of Bergmann and Gierth (*loc. cit.*) was slightly modified. 2-Chlorocyclohexanone (100 g.) was shaken (5 hours) with a solution of potassium carbonate (400 g.) in water (750 ml.). The solid obtained was washed, first with water (until chloride free) and then with three 50-ml. portions of ice-cold ether. After drying in a vacuum desiccator, pure (V) (69 g., 81%) was obtained, m. p. 112° (Bergmann and Gierth give m. p. 112—113°, Bouveault and Chereau, *Compt. rend.*, 1906, **142**, 1066, give m. p. 113°, and Kötz and Grethe, *J. pr. Chem.*, 1909, [ii], **80**, 488, give m. p. 92—92·5°). Difficulty is encountered if an attempt is made to crystallise the product from alcohol as suggested by some of the above authors.

Condensations in the Presence of Dilute Sulphuric Acid.—The ketone (V) (4 g.) was dissolved in ethyl alcohol (50 ml.) along with the appropriate hydrazine (1 mole), and the solution added to 2·5*N*-sulphuric acid (150 ml.). After refluxing (1 hour), the alcohol was distilled off and the product extracted with ether and crystallised from benzene. The yields are based on the amount of the phenylhydrazine used.

1-*Ketotetrahydrocarbazole*. Yield 71%. Colourless plates from benzene. M. p. and mixed m. p. with a sample prepared by the method of Coffey (*loc. cit.*) 168—169° (Found: C, 78·3; H, 6·0; N, 7·4. Calc. for $C_{12}H_{11}ON$: C, 77·9; H, 5·95; N, 7·6%). *Picrate*: light orange needles (from benzene), m. p. 167° (Found: C, 60·3; H, 4·1; N, 11·6. $2C_{12}H_{11}ON,C_6H_3O_7N_3$ requires C, 60·1; H, 4·2; N, 11·1%). *Semicarbazone*: colourless plates (from benzene), m. p. 228—230° (Found: C, 64·5; H, 6·0; N, 23·0. Calc. for $C_{13}H_{14}ON_4$: C, 64·5; H, 6·0; N, 23·1%). Coffey (*loc. cit.*) reports m. p. 228—230°. *p-Nitrophenylhydrazone*: dark red needles (from glacial acetic acid), m. p. 228—230° (Found: N, 12·5. $C_{18}H_{18}O_2N_4$ requires N, 12·5%).

1-*Keto-6-methyltetrahydrocarbazole*. Yield 71%. Colourless prisms, m. p. 194—195°, from benzene (lit., m. p. 195°, 195—196°) (Found: C, 78·3; H, 6·5; N, 7·3. Calc. for $C_{13}H_{13}ON$: C, 78·3; H, 6·5; N, 7·0%).

1-*Keto-6-methoxytetrahydrocarbazole*. Yield 89%. Colourless plates [from benzene–light petroleum (b. p. 40—60°)], m. p. 180—182° (decomp.) (Found: N, 5·9; OMe, 12·5. $C_{13}H_{13}O_2N,0·5C_6H_6$ requires N, 5·6; OMe, 12·3%).

1-*Keto-6-ethoxytetrahydrocarbazole*. Yield 74%. Colourless needles (from aqueous alcohol), m. p. 185—186° (Found: N, 6·05. $C_{14}H_{15}O_2N$ requires N, 6·1%).

Condensation in Ethyl Alcohol.—(V) (3 g.) was dissolved in ethyl alcohol (35 ml.), and phenylhydrazine (2·85 g., 1 mole) was added. After refluxing (15 hours), during which ammonia was evolved, the cooled solution deposited fine yellow needles of (VI) (1·30 g.; m. p. 153°). When the solution was concentrated (to *ca.* 8—10 ml.), a further quantity of (VI) (0·14 g.) was obtained. The filtrate was added to 2·5*N*-sulphuric acid (150 ml.) and extracted with ether. The ethereal extract was dissolved in a small volume of benzene and slowly added to light petroleum (b. p. 60—90°). The resultant amorphous precipitate was crystallised from benzene, yielding pure 1-ketotetrahydrocarbazole (0·45 g.; m. p. 169°). When the acidic solution was basified and extracted with ether, aniline (0·61 g.) [identified as its picrate, m. p. and mixed m. p. 163—165° (decomp.)] was obtained.

Condensation in the Presence of Glacial Acetic Acid.—(V) (3 g.) was dissolved in glacial acetic acid (25 ml.) and cooled to 0°. The appropriate phenylhydrazine was added and the mixture set aside for various times. The resultant osazone was filtered off. Only a very small amount of osazone was obtained from the filtrate. The table summarises the results obtained. The percentage yields are based on the weight of (V) used.

Substituted phenylhydrazine.	No. of moles per mole of (V).	Time.	Temp.	Yield of osazone, %.
(Unsubstituted)	1	1 hr.	0°	10
	2	,,	,,	42
	3	,,	,,	70
p-Tolyl	1 & 2	,,	,,	0
	3	,,	,,	16
	3	24 hrs.	20°	68
p-Chloro	1	1 hr.	0°	16
	3	,,	,,	72
p-Nitro	3	,,	,,	88
p-Methoxy ...	3	15 hrs.	20°	0 •

• Although no precipitate was formed, it was found that, when the glacial acetic acid was evaporated under reduced pressure and the residue treated with dilute sulphuric acid and extracted with ether, an 89% yield of 1-keto-6-methoxytetrahydrocarbazole (identical with the product from the dilute sulphuric acid condensation) was obtained.

The cyclohexane-1 : 2-dione bisphenylhydrazone formed yellow needles, m. p. 153°, from ethyl alcohol (Kötz, Blendermann, Rosenbusch, and Sirringhaus, *Annalen*, 1913, **400**, 67, report m. p. 150—151°, and Bergmann and Gierth, *loc. cit.*, report m. p. 153°) (Found: N, 19·1. Calc. for $C_{18}H_{20}N_4$: N, 19·1%). It gave a *picrate*, light orange needles (from benzene), m. p. 149° (Found: N, 19·0. $C_{18}H_{20}N_4,C_6H_3O_7N_3$ requires N, 18·8%), and *styphnate*, orange needles (from ethyl alcohol), m. p. 163° (decomp.) (Found: N, 18·0. $C_{18}H_{20}N_4,C_6H_3O_8N_3$ requires N, 18·2%).

The cyclo*hexane*-1 : 2-*dione bis-p-tolylhydrazone* formed yellow prisms, m. p. 136°, from ethyl alcohol (Found: N, 17·2. $C_{20}H_{24}N_4$ requires N, 17·4%).

The cyclo*hexane*-1 : 2-*dione bis*-p-*chlorophenylhydrazone* formed yellow needles (from ethyl alcohol), m. p. 196—197° (decomp.) (Found : N, 15·5. $C_{18}H_{18}N_4Cl_2$ requires N, 15·5%).

The cyclo*hexane*-1 : 2-*dione bis*-p-*nitrophenylhydrazone* formed bright red needles (from ethyl alcohol), m. p. 231° (decomp.) (Found : N, 21·4. $C_{18}H_{18}O_4N_6$ requires N, 22·0%).

When 2-chlorocyclohexanone (3 g.) was shaken in glacial acetic acid (25 ml.) at 0° for 1 hour with phenylhydrazine (1, 2, or 3 moles), (VI) was produced in yields of 0, 15, and 34% respectively. (The percentage yields are based on the weight of 2-chlorocyclohexanone used.)

Analyses are by Drs. Strauss and Weiler and Messrs. N. L. Lottkowitz and N. W. Gamble.

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270. *Aryl-2-halogenoalkylamines. Part VII. Some Derivatives of 2-Naphthyldi-2′-halogenoalkylamines.*

By W. DAVIS, J. L. EVERETT, and W. C. J. ROSS.

The preparation of certain derivatives of 2-naphthyldi-2′-halogenoalkylamines is described. The reactivity of the halogen atoms in these compounds—as measured by the rate of hydrolysis in aqueous acetone—is discussed.

THE preparation of a number of arykdi-2-halogenoalkylamines has already been described (Parts I and II, *J.*, 1949, 183, 1972). Many of these compounds have the property of inhibiting the growth of various animal tumours and of spontaneous and transmitted leukæmia in the Furth AK 1 pure line (Haddow, Kon, and Ross, *Nature*, 1948, **162**, 824). One of the compounds examined, 2-naphthyldi-2′-chloroethylamine, has been used clinically for the treatment of various lymphadenopathies in human patients with encouraging results. The present communication deals mainly with compounds related to this effective compound.

The compounds now described include the di-2′-chloroethyl derivatives of 6- and 8-methyl-, 8-ethyl-, 8-acetyl-, 1 : 2 : 3 : 4-tetrahydro-, and 5 : 6 : 7 : 8-tetrahydro-2-naphthylamine, and also of 2- and 3-aminophenanthrene which can be regarded as 5 : 6- and 7 : 8-benz-derivatives of 2-naphthylamine. Aryldi-2′-halogenoethylamines were prepared from the parent aromatic amines exactly as described in Part I.

6-Methyl-2-naphthylamine was obtained by the Bucherer reaction on the naphthol, which was prepared from the sulphonation product of 2-methylnaphthalene (Dziewonski, Schoenówna, and Waldmann, *Ber.*, 1925, **58**, 1212). 1-Keto-7-methoxy-1 : 2 : 3 : 4-tetrahydronaphthalene was converted into 8-methyl-2-naphthylamine as described by Haworth and Sheldrick (*J.*, 1934, 1950). Brown, Jacobs, Winsten, Levy, Moss, and Ott (*J. Org. Chem.*, 1946, **11**, 163) obtained an acetyl-2-naphthylamine, by a Friedel-Crafts reaction on 2-acetnaphthalide, which they regarded as 1-acetyl-2-naphthylamine but it was later shown to be the 8-acetyl derivative (Leonard and Hyson, *J. Org. Chem.*, 1948, **13**, 164). Reduction of 8-acetyl-2-naphthylamine by Huang-Minlon's modified Kishner–Wolff procedure (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) afforded 8-ethyl-2-naphthylamine which was characterised by the preparation of the *acetyl* derivative. A mixture of 5- and 6-nitro-1 : 2 : 3 : 4-tetrahydronaphthalene is obtained by the nitration of 1 : 2 : 3 : 4-tetrahydronaphthalene (Schroeter, *Annalen*, 1922, **426**, 39); this was readily resolved by a fractional distillation through an electrically heated column. Catalytic reduction of the nitro-compounds by using Raney nickel yielded the required 5 : 6 : 7 : 8-tetrahydronaphthylamines. 1 : 2 : 3 : 4-Tetrahydro-2-naphthylamine (*Org. Synth.*, Coll. Vol. I, p. 499) and 1 : 2 : 3 : 4-tetrahydro-1-naphthylamine, prepared by the reduction of 1-keto-1 : 2 : 3 : 4-tetrahydronaphthalene oxime with sodium and ethanol (compare von Braun, *Ber.*, 1922, **55**, 3648), were converted into the di-2-hydroxyethyl derivatives in the usual manner but it was found preferable to use thionyl chloride in chloroform solution for the chlorination stage. On one occasion the reaction between ethylene oxide and 1 : 2 : 3 : 4-tetrahydro-2-naphthylamine afforded a mixture of mono- and di-2′-hydroxyethyl derivatives which was resolved after conversion into the chloroethylamine hydrochlorides.

Bachmann and Boatner's method (*J. Amer. Chem. Soc.*, 1936, **58**, 2097) was used to prepare 2- and 3-aminophenanthrene.

For further confirmation of the finding that it is necessary to have two reactive groups in the molecule for growth-inhibitory activity *N*-2-naphthyl-*N*-methyl-2′-chloroethylamine and *N*-2-naphthyl-*N*-methyl-2′-chloro-*n*-propylamine were prepared. Both these compounds were inactive.

N′-Acetyl- and *N*′-benzoyl-*NN*-di-2-chloroethyl-*p*-phenylenediamine were described in

TABLE I.

Aryl-2-hydroxy- and -halogeno-alkylamines.

Compound.	M. p.	Crystal form.	S.	Formula.	Found, % C.	Found, % H.	Required, % C.	Required, % H.
2-*Methyl*-1-*naphthyldi*-2′-*chloroethyl*-*amine*	(Oil)	—	—	$C_{13}H_{19}NCl_2$	(Cl, 25·0)		(Cl, 25·1)	
1 : 2 : 3 : 4-*Tetrahydro*-1-*naphthyldi*-2′-*hydroxyethylamine*	89°	Prismatic needles	C–E	$C_{14}H_{21}O_2N$	71·5	9·2	71·5	9·0
1 : 2 : 3 : 4-*Tetrahydro*-1-*naphthyldi*-2′-*hydroxyethylamine picrate*	140	Sword-shaped	A	$C_{20}H_{24}O_9N_4$	51·6	5·4	51·7	5·2
1 : 2 : 3 : 4-*Tetrahydro*-1-*naphthyldi*-2′-*chloroethylamine hydrochloride*	158	Prismatic needles	B	$C_{14}H_{20}NCl_3$	54·3	6·5	54·5	6·5
5 : 6 : 7 : 8-*Tetrahydro*-1-*naphthyldi*-2′-*hydroxyethylamine picrate*	199 (decomp.)	Needles	A	$C_{20}H_{24}O_9N_4$	51·3	4·8	51·7	5·2
5 : 6 : 7 : 8-*Tetrahydro*-1-*naphthyldi*-2′-*chloroethylamine*	(Oil)	—	—	$C_{14}H_{19}NCl_2$	(Cl, 26·0)		(Cl, 26·1)	
5 : 6 : 7 : 8-*Tetrahydro*-1-*naphthyldi*-2′-*chloroethylamine picrate*	121	Plates	A	$C_{20}H_{22}O_7N_4Cl_2$	47·7	4·7	47·9	4·4
N-2-*Naphthyl*-N-*methyl*-2′-*hydroxyethylamine picrate*	160	Needles	B	$C_{19}H_{16}O_9N_4$	53·3	4·1	53·0	4·2
N-2-*Naphthyl*-N-*methyl*-2′-*chloroethylamine*	52·5	Needles	D	$C_{13}H_{14}NCl$	71·2	6·4	71·1	6·4
N-2-*Naphthyl*-N-*methyl*-2′-*hydroxy*-n-*propylamine picrate*	154	Needles	B	$C_{20}H_{20}O_9N_4$	54·0	4·5	54·1	4·5
N-2-*Naphthyl*-N-*methyl*-2′-*chloro*-n-*propylamine*	64	Needles	D	$C_{14}H_{16}NCl$	71·8	6·9	71·9	6·9
6-*Methyl*-2-*naphthyldi*-2′-*hydroxyethylamine*	94	Fine needles	C	$C_{15}H_{19}O_2N$	73·3	7·9	73·4	7·8
6-*Methyl*-2-*naphthyldi*-2′-*chloroethylamine*	65	Needles	D	$C_{13}H_{17}NCl_2$	63·8	6·0	63·9	6·1
6-*Methyl*-2-*naphthyldi*-2′-*bromoethylamine*	88	Rhombs	E	$C_{13}H_{17}NBr_2$	48·3	4·5	48·5	4·6
6-*Methyl*-2-*naphthyldi*-2′-*iodoethylamine*	100—101	Flattened needles	E	$C_{13}H_{17}NI_2$	29·3 (I, 55·0)	4·0	28·8 (I, 54·6)	3·7
8-*Methyl*-2-*naphthyldi*-2′-*chloroethylamine*	63	Prisms	D	$C_{13}H_{17}NCl_2$	63·9	6·2	63·9	6·1
8-*Ethyl*-2-*naphthyldi*-2′-*chloroethylamine*	48	Prismatic needles	D	$C_{14}H_{19}NCl_2$	65·1	6·7	64·9	6·5
8-*Ethyl*-2-*naphthyldi*-2′-*bromoethylamine*	57	Flattened rhombs	E	$C_{14}H_{19}NBr_2$	49·9	5·1	49·9	5·0
8-*Ethyl*-2-*naphthyldi*-2′-*iodoethylamine*	85	Prisms	D	$C_{14}H_{19}NI_2$	40·0 (I, 53·2)	3·8	40·1 (I, 53·0)	4·0
8-*Acetyl*-2-*naphthyldi*-2′-*hydroxyethylamine*	113	Yellow needles	C	$C_{14}H_{19}O_2N$	70·6	7·1	70·3	7·0
8-*Acetyl*-2-*naphthyldi*-2′-*chloroethylamine* [k]	84	Yellow needles	E	$C_{14}H_{17}ONCl_2$	62·2	5·4	61·9	5·5
8-*Acetyl*-2-*naphthyldi*-2′-*bromoethylamine* [k]	94·5	Yellow needles	E	$C_{14}H_{17}ONBr_2$	48·4	4·3	48·2	4·3
1 : 2 : 3 : 4-*Tetrahydro*-2-*naphthyl*-2′-*chloroethylamine hydrochloride*	215	Felted needles	A	$C_{12}H_{17}NCl_2$	58·1	7·1	58·5	6·9
1 : 2 : 3 : 4-*Tetrahydro*-2-*naphthyl*-2′-*chloroethylamine picrate*	197	Prismatic needles	B–F	$C_{18}H_{19}O_7N_4Cl$	49·3	4·1	49·3	4·3
1 : 2 : 3 : 4-Tetrahydro-2-naphthyldi-2′-hydroxyethylamine picrate [l]	142	Felted needles	A	$C_{20}H_{24}O_9N_4$	51·6	5·4	51·7	5·2
1 : 2 : 3 : 4-*Tetrahydro*-2-*naphthyldi*-2′-*chloroethylamine hydrochloride*	164	Small prisms	B	$C_{14}H_{20}NCl_3$	(Cl, 34·2)		(Cl, 34·5)	
1 : 2 : 3 : 4-*Tetrahydro*-2-*naphthyldi*-2′-*bromoethylamine hydrobromide*	229	Fine needles	B	$C_{14}H_{20}NBr_3$	(Br, 54·5)		(Br, 54·3)	
5 : 6 : 7 : 8-*Tetrahydro*-2-*naphthyldi*-2′-*hydroxyethylamine*	57	Needles	G	$C_{14}H_{21}O_2N$	71·5	9·0	71·5	9·0
5 : 6 : 7 : 8-*Tetrahydro*-2-*naphthyldi*-2′-*chloroethylamine* [l]	65	Prismatic needles	D	$C_{14}H_{19}NCl_2$	61·5	7·0	61·8	7·0
2-*Phenanthryldi*-2′-*hydroxyethylamine*	155	Plates	C–B	$C_{16}H_{15}O_2N$	77·1	6·9	76·8	6·8
2-*Phenanthryldi*-2′-*chloroethylamine*	91—92	Needles	E	$C_{16}H_{17}NCl_2$	67·7	5·5	67·9	5·4
2-*Phenanthryldi*-2′-*bromoethylamine*	111—112	Needles	E	$C_{16}H_{17}NBr_2$	53·3	4·4	53·1	4·2
2-*Phenanthryldi*-2′-*iodoethylamine*	117	Needles	E	$C_{16}H_{17}NI_2$	42·7	3·5	43·1	3·4
3-*Phenanthryldi*-2′-*hydroxyethylamine*	109—110	Plates	C	$C_{16}H_{15}O_2N$	76·9	6·9	76·8	6·8
3-*Phenanthryldi*-2′-*chloroethylamine*	73	Rhombs	E	$C_{16}H_{17}NCl_2$	68·1	5·4	67·9	5·4
3-*Phenanthryldi*-2′-*bromoethylamine*	98	Needles	E	$C_{16}H_{17}NBr_2$	52·7	3·9	53·1	4·2
3-*Phenanthryldi*-2′-*iodoethylamine*	125	Needles	E	$C_{16}H_{17}NI_2$	43·7	3·7	43·1	3·4
N-2′-Hydroxyethyl-2-aminofluorene [k]	150	Yellow plates	C	$C_{15}H_{15}ON$	79·6	6·7	80·0	6·7

TABLE I (*continued*).

Compound.	M. p.	Crystal form.	S.	Formula.	Found, % C.	Found, % H.	Required, % C.	Required, % H.
NN-*Di-2′-bromoethyl-2-aminofluorene*	137	Prismatic needles	C–E	$C_{17}H_{17}NBr_2$	52·0	4·5	51·7	4·3
N′-*Propionyl*-NN-*di-2-chloroethyl*-p-*phenylenediamine*	101—103	Prisms	E	$C_{13}H_{18}ON_2Cl_2$	53·9	6·4	54·0	6·3
NN-*Di-2-chloropropyl*-p-*aminobenzoic acid* [5]	165—166	Stout needles	A–H	$C_{13}H_{17}O_2NCl_2$	54·0	6·0	53·8	5·9
Methyl NN-*di-2-chloropropyl*-p-*aminobenzoate*	61	Needles	E	$C_{14}H_{19}O_2NCl_2$	55·6	6·2	55·3	6·3

Solvents (S) used for crystallisation are: A, methanol; B, ethanol; C, benzene; D, light petroleum (b. p. 40—60°); E, light petroleum (b. p. 60—80°); F, acetone; G, *cyclo*hexane; and H, water.

[3] Solutions of these compounds exhibit an intense yellow-green fluorescence. [4] Matskevich (*J. Gen. Chem. Russia*, 1941, **11**, 1023) reported m. p. 140°. [5] This compound is photoluminescent (cf. Part I). [6] In Part I the m. p. was given as 144—146°. [7] This acid was prepared by hydrolysing the product of the reaction between propylene oxide and ethyl *p*-aminobenzoate with concentrated hydrochloric acid (cf. Part II).

Part II; only the acetyl derivative was active. The active substance is probably the amine derived by hydrolysis of the acyl group and it would be expected that such hydrolysis would be more difficult in the case of the benzoate. Another derivative, *N′-propionyl*-NN-*di*-2-*chloroethyl*-p-*phenylenediamine*, has been prepared; this is also a very effective compound.

The reactivity of the halogen atoms in *NN*-di-2-chloroethyl-*p*-aminobenzoic acid is not of a high order (Part I) and so to obtain a more reactive acidic compound the corresponding *di-2-chloro*-n-*propyl* derivative and its methyl ester have been prepared. For the same reason the *bromo*-compound corresponding to the feebly active *NN*-di-2′-chloroethyl-2-aminofluorene was examined.

The preparation of *N*-2′-chloroethyl-2-aminofluorene (cf. Part I) has been re-examined. *N*-2′-Hydroxyethyl-2-aminofluorene, prepared as previously described, was obtained in purer form after a chromatographic purification of the reaction product. Chlorination of this hydroxy-compound presented difficulties on a larger scale but a satisfactory method using phosphorus pentachloride in chloroform solution at low temperature was eventually evolved.

Peters and Wakelin (*Biochem. J.*, 1947, **41**, 545) have shown that the potentiating action of sodium diethyldithiocarbamate on the action of di-2-chloroethyl sulphide is due to the formation of an ester derivative. When *NN*-di-2-chloroethyl-*p*-anisidine was allowed to react in a solution containing sodium diethyldithiocarbamate NN-*di*-2-(*diethyldithiocarbamatoethyl*)-p-*anisidine* was formed; the chloroethyl(diethyldithiocarbamatoethyl) derivative was not isolated. The disubstituted compound, like the corresponding derivative of "mustard gas," was less toxic than the parent halide, no doubt owing to the fact that it no longer possesses an active halogen atom. The increased toxicity of the monosubstituted product obtained by Peters and Wakelin is almost certainly due to the increased reactivity of the remaining halogen atom which would be expected if one chlorine atom was replaced by a sulphur-containing group. Such an increase in the reactivity of the second halogen atom is indicated in Ogston's experiments (*Trans. Faraday Soc.*, 1948, **44**, 45) in which mustard gas reacts with various thio-esters.

A consideration of the reactions of aryldi-2-halogenoalkylamines suggested that when they reacted with naturally occurring substances under mild conditions, they could be regarded as difunctional electrophilic reagents. Under similar conditions epoxides may be regarded as electrophilic reagents (Hammett, "Physical Organic Chemistry," New York, 1940, p. 301) and it therefore seemed of interest to examine a number of diepoxides. The first compound of this type to be tested, NN-*di*-(2 : 3-*epoxypropyl*)-p-*anisidine*, was prepared by the action of sodium hydroxide on *NN*-di-(3-chloro-2-hydroxy-*n*-propyl)-*p*-anisidine (Part II). Whilst this substance was not effective, a number of more reactive diepoxides including 1 : 2-3 : 4-diepoxybutane, 1 : 2-5 : 6-diepoxyhexane, di-2 : 3-epoxypropyl ether, and 1 : 4-di-(2′ : 3′-epoxypropoxy)-benzene do induce the formation of chromosome abnormalities and inhibit the growth of transplanted tumours in a manner indistinguishable from that characteristic of the "mustards." Monoepoxides, for example, propylene oxide, epichlorohydrin, and *cyclo*hexene oxide, appear to be inactive as tumour-growth inhibitors.

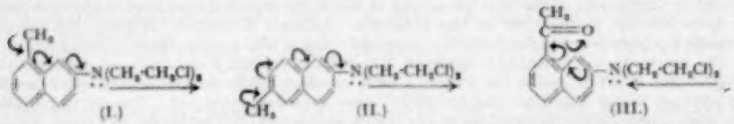
A list of the compounds prepared in this work is given in Table I.

Table II shows the rate of hydrolysis of a number of the halogenoalkylamines in unbuffered 50% aqueous acetone at 66°. Many of the compounds now prepared are less soluble than those

examined in Parts I and II and had to be hydrolysed at higher dilutions than in the standard procedure. Since the hydrolysis proceeds by an S_N1 mechanism the effect of dilution is merely to reduce the extent of the bimolecular back reaction with halide ions and so the values obtained in more dilute solutions are relatively higher (see below).

The influence of dilution on the rate of hydrolysis of *NN*-di-2-chloroethyl-*p*-anisidine was shown in Part I. 58% Hydrolysis occurred at 66° when 0·5 millimol. of amine was dissolved in 50 ml. of 50% aqueous acetone; 64% when the volume was 100 ml.; and 67% in 320 ml. The effect is most marked at higher concentrations and it is not serious when 0·5 millimol. of the amine is dissolved in 100 ml. or more of 50% aqueous acetone. Since most of the hydrolysis rates given in Table II had to be measured at higher dilutions no great error is made in comparing the values as in the discussion below.

A 2-methyl substituent in the 1-naphthylamine derivative causes an appreciable increase in the reactivity of the chlorine atom. The substitution of the hydrogen atoms in the 6- and 8-positions of the 2-naphthylamine nucleus by methyl groups results in a significantly higher rate of hydrolysis of the di-2′-chloroethyl derivatives whereas an 8-ethyl substituent has little effect on the reactivity of the halogen in the dichloro-, dibromo-, or di-iodo-ethylamine. The effect of the 6- and 8-methyl groups would have been expected since they could increase the electron availability on the nitrogen atom which in turn would activate the halogen atoms (I—II):



The bond structure of the naphthalene nucleus shown in (I), (II), and (III) is only one of the possible forms and it is interesting to note that the effect of the methyl group is greater in the aniline derivative (Part I) where the two predominating possible structures (IV) and (V) both permit activation of the halogen atom:

The hydrolysis rate of the *p*-toluidine derivative is 38% and that of the aniline derivative 20%.

The electron-release effect of the ethyl group is less than that of the methyl group in a system such as that under consideration [compare the relative basicities of *NN*-dimethyl-*p*-toluidine (pK_a 4·77) and *NN*-dimethyl-*p*-ethylaniline (pK_a 4·69); Davies, *J.*, 1938, 1865]; this is reflected in the negligible effect of the 8-ethyl substituent.

An 8-acetyl substituent has an appreciable deactivating effect on the halogen in both the 2′-chloro- and the 2′-bromo-ethylamines; this would be expected in view of the electron-attracting capacity of the acetyl group as demonstrated in (III).

5 : 6 : 7 : 8-Tetrahydro-2-naphthyldi-2′-chloroethylamine can be regarded as the aniline compound with alkyl substituents in the *m*- and *p*-positions. A *m*-methyl group has little effect on the activity of the halogen atom in the aniline derivative (hydrolysis rates: *NN*-di-2-chloroethylaniline, 20%; *NN*-di-2-chloroethyl-*m*-toluidine, 21%; *NN*-di-2-chloroethyl-*p*-toluidine, 38%), but a *p*-methyl group causes a considerable increase. This is quite comparable to the effect of fusing the alicyclic ring as in this tetrahydro-compound. In 5 : 6 : 7 : 8-tetrahydro-1-naphthyldi-2′-chloroethylamine the alicyclic ring can be likened to *o*- and *m*-substituents and again the effect is comparable for *NN*-di-2-chloroethyl-*o*-toluidine has a hydrolysis rate of 83%.

The fusion of an aromatic ring system to the 3 : 4-position of the aniline nucleus—giving the 2-naphthyl derivative—causes a decrease in the reactivity of the halogen atom. For the chloro-compounds the decrease is from 20% to 15% hydrolysis and whilst the bromo-derivatives hydrolyse at about the same rate (80%) the value for the 2-naphthyl compound was determined at a higher dilution and is therefore relatively high. A similar decrease in the reactivity of the halogens is produced when benzene rings are fused on to the 5 : 6- or 7 : 8-positions of the 2-naphthyl nucleus. In the case of each of the halogenoethyl derivatives of the phenanthryl-amines the hydrolysis rates had to be determined at higher dilutions but this only serves to

emphasise the effect of the substituent for had the rates been measured at the same dilution the depression of the reactivity of the halogen atom must have been more marked.

TABLE II.

Compound (0·5 millimoles).	Volume of acetone : water (ml.).	% Hydrolysis in 30 mins. at 66°.[a]	
1-Naphthyldi-2′-chloroethylamine	30 : 30	50	
2-Methyl-1-naphthyldi-2′-chloroethylamine	50 : 50	75	
2-Naphthyldi-2′-chloroethylamine	25 : 25	15	
2-Naphthyldi-2′-bromoethylamine	55 : 55	80	
2-Naphthyldi-2′-iodoethylamine	70 : 70	64	
2-Naphthyldi-2′-chloro-*n*-propylamine	35 : 35	86	
N-2-Naphthyl-*N*-methyl-2′-chloroethylamine	25 : 25	25	
N-2-Naphthyl-*N*-methyl-2′-chloro-*n*-propylamine	25 : 25	87	
6-Methyl-2-naphthyldi-2′-chloroethylamine	50 : 50	24	
6-Methyl-2-naphthyldi-2′-bromoethylamine	50 : 50	85	
6-Methyl-2-naphthyldi-2′-iodoethylamine	70 : 70	74	
8-Methyl-2-naphthyldi-2′-chloroethylamine	50 : 50	21	
8-Ethyl-2-naphthyldi-2′-chloroethylamine	50 : 50	14	
8-Ethyl-2-naphthyldi-2′-bromoethylamine	70 : 70	84	
8-Ethyl-2-naphthyldi-2′-iodoethylamine	75 : 75	66	
8-Acetyl-2-naphthyldi-2′-chloroethylamine	50 : 50	4	
8-Acetyl-2-naphthyldi-2′-bromoethylamine	50 : 50	45	
5 : 6 : 7 : 8-Tetrahydro-2-naphthyldi-2′-chloroethylamine	50 : 50	44	
5 : 6 : 7 : 8-Tetrahydro-1-naphthyldi-2′-chloroethylamine	60 : 60	86	
2-Phenanthryldi-2′-chloroethylamine	75 : 75	9	
2-Phenanthryldi-2′-bromoethylamine	100 : 100	79	
2-Phenanthryldi-2′-iodoethylamine	300 : 300	52	
3-Phenanthryldi-2′-chloroethylamine	75 : 75	11	
3-Phenanthryldi-2′-bromoethylamine	75 : 75	76	
3-Phenanthryldi-2′-iodoethylamine	300 : 300	54	
NN-Di-2′-chloroethyl-2-aminofluorene	100 : 100	26	
NN-Di-2′-bromoethyl-2-aminofluorene	100 : 100	90	
		H, %.	Cl, %.[b]
1 : 2 : 3 : 4-Tetrahydro-1-naphthyldi-2′-chloroethylamine	50 : 50	89	98
1 : 2 : 3 : 4-Tetrahydro-2-naphthyldi-2′-chloroethylamine	50 : 50	70	83
1 : 2 : 3 : 4-Tetrahydro-2-naphthyldi-2′-bromoethylamine	85 : 85	—	100
Methyldi-2-chloroethylamine	25 : 25	44	84
Dimethyl-2-chloroethylamine	25 : 25	11	97
Di-2-chloroethyl sulphide	25 : 25	100	100
Ethyl 2-chloroethyl sulphide	25 : 25	89	100

[a] In the first series of derivatives of aromatic amines the chloride and the hydrogen-ion titre after hydrolysis were identical. [b] In the second series of derivatives of aliphatic amines the two titres sometimes differed (see discussion). The figures are based on complete hydrolysis.

TABLE III.

Hydrolysis of 2-naphthyldi-2′-halogenoethylamines in 66% acetone (*a*) alone and (*b*) in the presence of sodium thiosulphate (0·0066M.). Concn. of amine, 0·00166M.; Temp., 37°; Time, 2 hours.

Compound.	(*a*) % Hydrolysis.	(*b*) % consumption of thiosulphate.
2-Naphthyldi-2′-chloroethylamine	2	4
2-Naphthyldi-2′-bromoethylamine	18	44
2-Naphthyldi-2′-iodoethylamine	9	65

(*a*) and (*b*) are based on the complete reaction of the halides.

Table II shows four complete series of chloro-, bromo-, and iodo-ethylamines—those of 2-naphthylamine, 6-methyl-2-naphthylamine, and 2- and 3-phenanthrylamines. In each instance there is the expected increase in the rate of hydrolysis on passing from the chlorides to the bromides but then a somewhat surprising decrease for the iodides. It would be expected that the extent of ionisation of the iodide ion from the 2′-carbon atom would be greater than that of the bromide ion. Since it is known that the competition factor of the iodide ion for the carbonium ion is much higher than that of either the chloride or bromide ion (Part III, *J.*, 1949, 2589, and Ogston, *loc. cit.*) it was thought possible that the apparently slower rate of hydrolysis of the iodides might be due to a relatively faster bimolecular, back reaction whereby halide is re-formed, rather than to a slower rate of ionisation. If the hydrolyses are carried out in the presence of an excess of sodium thiosulphate the rate of consumption of thiosulphate can be regarded as a measure of the rate of formation of carbonium ion (Part III). When 8-ethyl-2-naphthyldi-2′-halogenoethylamines are hydrolysed as recorded in Table II but with the

addition of thiosulphate, the extent of carbonium-ion formation is found to be: chloro-compound, 17%; bromo-compound, 100%; and iodo-compound, 100%. It is therefore clear that the differences in the values for the bromo- and iodo-derivatives given in Table II must be due to a difference in the degree of the back reaction. A further series of experiments in which 2-naphthyldi-2′-halogenoethylamines were hydrolysed in 66% aqueous acetone at 37° showed that, under these conditions, the iodo-compound does actually ionise faster than the corresponding bromo-compound (Table III).

The second section of Table II gives the rate of production of hydrogen and chloride ions from tetrahydronaphthyldi-2′-halogenoethylamines, which may be regarded as derivatives of aliphatic amines. As with the simple aliphatic "nitrogen mustards" the rate of production of the two ions is not identical and the difference in the values can be ascribed to the formation of quaternary nitrogen compounds—either an ethyleneimonium ion or a piperazine dimer (Golumbic, Fruton, and Bergmann, *J. Org. Chem.*, 1946, **11**, 518; Hanby, Hartley, Powell, and Rydon, *J.*, 1947, 520).

When methyldi-2-chloroethylamine (pK_a 6·45) is hydrolysed under the standard conditions the reaction stops when about one-half of the halogen has been eliminated; this is probably due to the fact that the pH change caused by the elimination of one equivalent of hydrochloric acid leads to the stabilisation of the chlorohydrin (pK_a 7·5) by salt formation. Dimethyl-2-chloroethylamine (pK_a 8·6) gives an almost total elimination of chloride ion but only about 10% of the theoretical acidity is developed. This means that only one-tenth of the carbonium ion formed reacts with water. These results can be interpreted if it is assumed that the base competes with water for reaction with the carbonium ion. Since a stronger base will compete more efficiently, more quaternary salt is formed in the case of the dimethylamine derivative. The tetrahydronaphthylamine derivatives being weaker bases compete less effectively and only about 10% of quaternary salt is formed. There is no indication of sulphonium-salt formation in the hydrolysis of di-2-chloroethyl sulphide in aqueous acetone, but about 10% of sulphonium salt is formed in the case of ethyl chloroethyl sulphide. At physiological pH (about 7·5) approximately 90% of dimethyl-2-chloroethylamine will be in the form of an ammonium cation which cannot yield a carbonium ion, and of the molecules yielding such an ion a high proportion will not be available for reaction with functional centres in the biological systems because of quaternary-salt formation. This should be borne in mind when conclusions are drawn from the fact that this compound is biologically inactive whereas the corresponding difunctional compound, which will be more reactive towards external centres, is effective. These objections would not appear to apply to the derivatives of aromatic amines which are much weaker bases (for example, *NN*-di-2-chloroethylaniline, pK_a 2·2; *N*-ethyl-*N*-2-chloroethylaniline, pK_a 3·5) or to the chloroethyl sulphides.

Experimental.

8-Ethyl-2-naphthylamine.—8-Acetyl-2-naphthylamine (Brown *et al.*, *loc. cit.*) (16 g.) was added to a cooled solution of sodium hydroxide (11·2 g.) and hydrazine hydrate (18·4 ml.; 50% solution) in diethylene glycol (175 ml.) contained in a flask carrying a short air condenser. The mixture was gradually heated to 195°. After 3 hours at this temperature the solution was cooled and extracted with ether. 8-Ethyl-2-naphthylamine (14·5 g.) was obtained as a brown oil when the dried extract was distilled. When a benzene solution of the amine was warmed with a slight excess of acetic anhydride the *acetyl* derivative, m. p. 167°, was formed (Found: C, 79·1; H, 7·2. $C_{14}H_{15}ON$ requires C, 78·8; H, 7·1%).

5- and 6-Nitro-1 : 2 : 3 : 4-tetrahydronaphthalene. 1 : 2 : 3 : 4-Tetrahydronaphthalene (264 g.) was nitrated as described by Schroeter (*loc. cit.*). The cooled nitration mixture was extracted with benzene (1500 ml.), and the washed and dried extract was allowed to percolate through a long column of activated alumina. Evaporation of the eluates gave a pale brown oil which was distilled (under reduced pressure) and the fraction, b. p. 140—180°/15 mm., was redistilled in a Towers fractional distillation unit, incorporating an electrically heated column and a variable take-off head. Three sharply separated fractions were obtained: (*a*) unchanged tetrahydronaphthalene, b. p. 90°/3 mm.; (*b*) 5-nitro-1 : 2 : 3 : 4-tetrahydronaphthalene, b. p. 154°/7 mm. (60 g.; m. p. 33°) (Schroeter gives m. p. 34°); and (*c*) 6-nitro-1 : 2 : 3 : 4-tetrahydronaphthalene, b. p. 158°/7 mm. (45 g.; m. p. 31·5°) (Schroeter gives m. p. 31·4°).

5 : 6 : 7 : 8-Tetrahydro-1- and -2-naphthylamine.—The nitro-compound (50 g.) dissolved in ethanol (200 ml.) containing Raney nickel catalyst (10 g.) was shaken in an atmosphere of hydrogen, at a pressure slightly greater than atmospheric, until the theoretical volume of gas was absorbed. After the addition of a slight excess of concentrated hydrochloric acid to the filtered solution it was concentrated under reduced pressure. The colourless plates of the hydrochloride which separated were dissolved in water and the base, liberated by addition of 2N-sodium hydroxide, was extracted with ether. After being dried over potassium hydroxide the amine was distilled; in this way 5 : 6 : 7 : 8-tetrahydro-1-naphthylamine (30 g.), b. p. 114°/3 mm., and 5 : 6 : 7 : 8-tetrahydro-2-naphthylamine (33 g.), b. p. 115°/4 mm., were obtained from the corresponding nitrotetrahydronaphthalenes.

1 : 2 : 3 : 4-Tetrahydro-1-naphthylamine.—Sodium (63 g. in small pieces) was added to a solution of 1-keto-1 : 2 : 3 : 4-tetrahydronaphthalene oxime (38 g.) in ethanol (500 ml.) at such a rate that the

mixture was kept refluxing gently. After the addition of water (600 ml.) the mixture was steam-distilled, the distillate being collected in a receiver containing hydrochloric acid (80 ml.; 5*N*.). When this solution was concentrated and cooled crystals of the amine hydrochloride separated; these were dissolved in water and the base was liberated by adding potassium hydroxide. The tetrahydronaphthylamine was obtained as a colourless viscous liquid when distilled in an atmosphere of hydrogen; it had b. p. 114°/10 mm. (Bamberger and Bammann, *Ber.*, 1889, **22**, 951, give b. p. 246·5°/714 mm.).

Halogenation of ac-*Tetrahydronaphthylal-2-hydroxyethylamines.*—The hydroxyethyl compound (0·1 mole) dissolved in chloroform (50 ml.) was added to a solution of thionyl chloride (or bromide) (0·2 mole) in chloroform (50 ml.) and the mixture was heated under reflux for one hour. The residue obtained after removal of the solvent under reduced pressure was crystallised from ethanol (charcoal) and gave the hydrochloride or hydrobromide of the chloroethylamine.

N-2′-*Chloroethyl*-2-*aminofluorene.*—2-Aminofluorene (11·1 g.), ethylene oxide (3·1 ml.), and benzene (10 ml.) were heated in a sealed tube at 90° for 8 hours. The product was diluted with benzene and the solution allowed to percolate down a long column of activated alumina. The early eluates contained unchanged amine but on developing the chromatogram with fresh benzene *N*-2′-hydroxyethyl-2-aminofluorene was obtained. The hydroxy-compound (3 g.) was dissolved in chloroform [150 ml.; dried ($CaCl_2$)] and to the ice-cooled solution phosphorus pentachloride (10 g.) was added slowly with shaking. After being kept in the ice-chest overnight the clear solution was poured on crushed ice, and the residue obtained by evaporating the dried chloroform layer was dissolved in benzene and allowed to percolate through a short column of alumina. The eluates contained the chloro-compound which formed prisms, m. p. 127°, from light petroleum (b. p. 60—80°).

NN-Di-2-(*diethyldithiocarbamatoethyl*)-p-*anisidine.*—*NN*-Di-2-chloroethyl-*p*-anisidine (2·5 g.) dissolved in 50% aqueous acetone (200 ml.) containing sodium diethyldithiocarbamate (3·4 g.) was heated under reflux for 2 hours. The oil which separated after removal of the acetone under reduced pressure was dissolved in benzene and purified chromatographically. *NN-Di*-2-*diethyldithiocarbamatoethyl*-p-*anisidine* formed thick prismatic needles, m. p. 85—86°, from ether or light petroleum (b. p. 40—60°) (Found: C, 53·6; H, 7·5. $C_{21}H_{33}ON_3S_4$ requires C, 53·2; H, 7·4%).

NN-Di-2 : 3-*epoxypropyl*-p-*anisidine.*—*NN*-Di-3-chloro-2-hydroxy-*n*-propyl-*p*-anisidine (40 g.) was suspended in dry ether (500 ml.) and the mixture gently refluxed whilst finely powdered potassium hydroxide (40 g.) was slowly added. After one hour all the amine had dissolved; the solution was filtered and evaporated, and the residue dissolved in benzene and then shaken with activated alumina (20 g.). The *anisidine* distilled as a yellow oil, b. p. 228—229°/9 mm. (Found: C, 66·7; H, 7·3. $C_{13}H_{17}O_3N$ requires C, 66·3; H, 7·3%).

Hydrolysis of Chloroethylamines.—The hydrolysis rates given in Table II were determined exactly as described in Part I and reactions in the presence of sodium thiosulphate were carried out by adding the required amount of the salt to the water before mixing with acetone; otherwise the conditions were the same. The thiosulphate consumption was followed by titration of an aliquot, diluted with twice its volume of water, with 0·1*N*-iodine solution (starch indicator).

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271. *The Configuration of Naturally Occurring Mixed Glycerides. Part VI. The Component Fatty Acids and Glycerides of Stillingia Tallows.*

By S. S. GUPTA and M. L. MEARA.

The component acids of two specimens of the tallow encasing the seeds of *Sapium sebiferum* (one from Hong Kong, the other from South Texas), and also the component acids of a specimen of tallow from *Sapium discolor* have been found to be, respectively: lauric, —, 1·5, —; myristic, 0·5, 3·4, 1·7; palmitic, 63·2, 72·1, 46·8; stearic, 7·6, 1·6, 2·0; oleic, 27·1, 20·4, 46·4; linoleic, 1·6, 1·0, 3·1% (by weight).

The chief component glycerides occurring in the Hong Kong specimens of *Sapium sebiferum* and *Sapium discolor* are respectively: *S. sebiferum*, oleodipalmitin, 64, stearodipalmitin 13, tripalmitin 8, and oleopalmitostearin 8%, with very small amounts of oleomyristopalmitin, linoleodipalmitin, and palmito-oleolinolein; *S. discolor*, oleodipalmitin 51, palmitodiolein 29, palmito-oleolinolein 6, oleomyristopalmitin 5, oleopalmitostearin 5%, with very small proportions of oleomyristostearin, linoleomyristopalmitin, linoleodiolein, and traces of triolein.

The stearodipalmitin and the oleodipalmitin occurring in *Sapium sebiferum* have been shown to occur exclusively as the symmetrical isomers.

Computation of the component glycerides from the component fatty acids by application of the rule of even distribution gives values in tolerable accordance with the observed values.

CHINESE vegetable tallow or Stillingia tallow is a hard fat, coating the seeds of the Chinese tallow tree [*Stillingia sebifera*, Willd. syn. *Sapium sebiferum* Roxb. (Euphorbiaceæ)], indigenous

to China but also grown in India, Japan, and other subtropical countries. The tree has been exploited for the leaves, from which was obtained colouring matter for dyeing silk, and for the seed oil, the separation of the tallow representing a secondary product. The tree grows to a height of about 40 feet, commences to bear fruit at 4—5 years and when fully grown produces 25—30 kg. of seed per annum.

The fruit consists of a 3-lobed capsule, each lobe containing an oval seed, average weight 0·125 g., which is surrounded by a thick (white) tallow-like mass filling the space in each cavity. The seeds consist of 70% of shell and 30% of kernel, the shell being coated with up to 30% of tallow and the kernels containing about 60% of a drying oil of entirely different constitution from that of the vegetable tallow (Hilditch, *J. Oil Col. Chem. Assoc.*, 1949, **32**, 5).

Two samples of tallow from *Sapium sebiferum* were used in the present investigation. The first was obtained from fruit, from trees growing in Hong Kong, which had been placed at our disposal by Dr. G. A. C. Herklots and Mr. I. P. Tamworth of the Development Secretariat, Hong Kong, and the second from trees growing in South Texas and placed at our disposal by Mr. J. Q. Wood of Oklahoma, U.S.A. The surface of the tallow coating of the latter specimen was black, apparently owing to a mould growth but this blackening did not penetrate below the surface layers.

The Hong Kong authorities also made available to us a specimen of the fruit of *Sapium discolor*, a closely related species. The fruit and seeds of this species are very similar in general appearance to those of *Sapium sebiferum* except that the capsule is somewhat thicker, the seeds are smaller (average weight 0·042 g.), and the surface of the tallow layer encasing the kernel shell is greenish white.

Discussion.

A survey of the literature reveals that Stillingia tallow is of relatively simple composition, the only major component fatty acids being palmitic and oleic. Somewhat wide divergence in the proportions of these acids has been reported, as is indicated by the observed range in iodine value (10—36) of the fat. This range may in some cases (especially in commercial samples) be due to incomplete extraction of the fat, or to the extraction of a small amount of the kernel oil. Potts and Bolley (*Oil and Soap*, 1946, **23**, 316) have recorded data for uncontaminated samples of the tallow from *Sapium sebiferum* grown in Texas, the iodine values of which range from 10·5 to 25·0. This observation, taken in conjunction with the data obtained by Hilditch and Priestman (*J. Soc. Chem. Ind.*, 1930, **49**, 397T), and with results obtained in the present investigation (Table I), indicates that the tree appears to be able to produce tallow of somewhat variable composition. The tallow from *Sapium discolor* has a considerably higher oleic acid content that that from *Sapium sebiferum* (see Table I).

Table I.

Component fatty acids of Stillingia tallows.

	Sapium sebiferum.						*Sapium discolor.*
	U.S.A.,*		Chinese,*		Hong Kong,†	South Texas,†	Hong Kong,†
	crude.	neutralised.	crude.	neutralised.	neutral.	crude.	neutralised.
Lauric	1·9	1·2	0·8	2·5	—	1·5	—
Myristic	3·7	2·9	5·8	3·6	0·5	3·4	1·7
Palmitic	66·3	63·1	69·6	57·6	63·2	72·1	46·8
Stearic	1·2	3·2	3·1	1·8	7·6	1·6	2·0
Oleic	26·9	29·6	20·7	34·5	27·1	20·4	46·4
Linoleic	—	—	—	—	1·6	1·0	3·1

* Hilditch and Priestman (*loc. cit.*). † Present investigation.

It is evident from Table I that the unsaturation of *Sapium discolor* tallow is considerably greater than that of the *Sapium sebiferum* fruit-coat fat, and that the increased unsaturation is due almost entirely to an increase in the oleic acid content of the tallow at the expense of palmitic acid, and (in the Hong Kong specimen) of stearic acid. The linoleic acid content rises only from 1·5 to 3·0%. It may be noted, however, that the stearic acid content of the Hong Kong specimen of *Sapium sebiferum* fruit-coat fat is distinctly higher than that recorded for other samples of this species by Hilditch and Priestman, and that the use of low-temperature crystallisation and spectrophotometry has indicated the presence of a small but significant linoleic acid content.

TABLE II.

Component fatty acids and glycerides of Sapium sebiferum *fruit-coat fat. Fractions obtained by crystallisation of fat.*

	A.	*B.*	*C.*	*D.*	Total.	
Wt. (g.)	21·82	8·02	60·01	9·85	100·6	
I.V.	1·6	28·4	31·3	44·4	26·0	
Sap. equiv.	274·5	281·7	279·3	278·7	278·3	
Glycerides, % (wt.)	21·7	8·9	59·6	9·8	100·0	
,, % (mol.)	22·0	8·8	59·4	9·8	100·0	
Component acids (increments, mol.-%) :					% (mol.).	% (wt.).
Myristic	—	—	0·6	—	0·6	0·5
Palmitic	17·4	5·2	36·8	6·0	65·4	63·2
Stearic	4·2	0·8	2·1	—	7·1	7·6
Oleic	0·4	2·8	19·4	2·9	25·5	27·1
Linoleic	—	—	0·5	0·9	1·4	1·6
Component glyceride categories (increments, mol.-%) :						
(i) Fully saturated	20·8	0·5	—	—	21·3	
Disatd. mono-unsatd.	1·2	8·3	59·1	8·0	76·6	
Monosatd. di-unsatd.	—	—	0·3	1·8	2·1	
Tri-unsaturated	—	—	—	—	—	
(ii) Monopalmito-	—	1·8	8·4	1·8	12·0	
Dipalmito-	13·8	7·0	51·0	8·0	79·8	
Tripalmitin	8·2	—	—	—	8·2	
(iii) No oleo-	20·8	0·5	1·3	1·0	23·6	
Mono-oleo-	1·2	8·3	58·1	8·8	76·4	
Dioleo-	—	—	—	—	—	
Triolein	—	—	—	—	—	
Possible component glycerides (increments, mol.-%) :						
Fully saturated (21·3%)						
Tripalmitin	8·2	—	—	—	8·2	
Stearodipalmitin	12·6	0·5	—	—	13·1	
Mono-" oleo " glycerides (76·6%)						
Oleomyristopalmitin	—	—	1·8	—	1·8	
Oleodipalmitin	1·2	6·5	49·7	7·0	64·4	
Linoleodipalmitin	—	—	1·3	1·0	2·3	
Oleopalmitostearin	—	1·8	6·3	—	8·1	
Di-" oleo " glycerides (2·1%)						
Palmito-oleolinolein	—	—	0·3	1·8	2·1	

Component Glycerides of Stillingia tallow.—(a) Sapium sebiferum *seed from Hong Kong.* In computing the glycerides present in fractions *A* and *B* (the fractions containing the bulk of the fully saturated glycerides, and the residual fully-saturated glycerides together with mono-oleo-glycerides, respectively, cf. Experimental) the unsaturation is considered to be present only in the form of mono-unsaturated disaturated glycerides, this being a necessary consequence of the fractional crystallisation. Similarly, fully saturated glycerides are assumed to be absent from fractions *C* and *D* (cf. Experimental) the components consisting of mono-" oleo " and di-" oleo " glycerides.

It is possible in most cases to consider the component glyceride categories present in an oil or fat in a number of ways. Taking into account component glyceride categories with respect to (i) unsaturation, (ii) palmitic acid distribution, (iii) oleic acid distribution, and considering these simultaneously and in conjunction with the component fatty acids of each fraction it is possible in this case to arrive at an accurate estimate of the probable component glycerides of the stillingia tallow.

This specimen of *S. sebiferum* tallow is thus a remarkably simple fat, two glycerides alone, namely stearodipalmitin and oleodipalmitin together constituting about 77% of the whole fat, and no other glyceride present occurring to the extent of more than 8%.

Sufficient material was available from fractions *A* and *C*, respectively, to permit investigation of the configuration of the mixed triglycerides occurring in these fractions. Crystallisation of a portion of fraction *A* from ether at high dilution gave rise to a fraction (60% of the whole) melting at 66·5—67°, this being a fairly pure specimen of β-stearo-αα′-dipalmitin (m. p. 68°), 16% of a mixture of β-stearo-αα′-dipalmitin and tripalmitin (m. p. 65—66°), and 20% of fairly pure tripalmitin (m. p. 64·5—65°) (65·5°, literature). There appears to be no evidence of the unsymmetrical α-stearo-α′β-dipalmitin (m. p. 63°) occurring in this fat.

TABLE III.

Component fatty acids and glycerides of Sapium discolor *fruit-coat fat. Fractions obtained by crystallisation of neutral fat.*

	A.	*B.*	*C.*	*D.*	Total.	
Wt. (g.)	25·31	32·61	31·08	8·52	97·52	
I.V.	31·4	32·3	61·4	83·6	45·8	
Sap. equiv.	278·0	277·6	286·1	315·5	283·3	
Glycerides, % (wt.)	25·9	33·5	31·9	8·7	100·0	
Glycerides, % (mol.)	26·5	34·1	31·6	7·8	100·0	
Component acids (increments, mol.-%) :					% (mol.).	% (wt.).
Myristic	—	1·3	0·7	—	2·0	1·7
Palmitic	17·1	20·1	10·3	1·5	49·0	46·8
Stearic	0·4	1·0	0·5	—	1·9	2·0
Oleic	8·9	11·3	18·5	5·4	44·1	46·4
Linoleic	0·1	0·4	1·6	0·9	3·0	3·1
Component glyceride categories (increments, mol.-%) :						
(i) Disatd. mono-unsatd.	26·0	33·3	2·6	—	61·9	
Monosatd. di-unsatd.	0·5	0·8	29·0	4·5	34·8	
Tri-unsaturated	—	—	—	3·3	3·3	
(ii) Monopalmito-	1·8	7·7	30·8	4·5	44·8	
Dipalmito-	24·7	26·4	—	—	51·1	
(iii) Mono-oleo-	26·2	33·8	7·7	—	67·7	
Dioleo-	0·3	—	23·9	7·1	31·3	
Triolein	—	—	—	0·7	0·7	
Probable component glycerides (increments, mol.-%) :						
Mono-" oleo " glycerides (61·9%)						
Oleomyristopalmitin	—	3·7	1·2	—	4·9	
Oleomyristostearin	—	—	0·8	—	0·8	
Oleopalmitostearin	1·2	3·0	0·7	—	4·9	
Oleodipalmitin	24·7	26·3	—	—	51·0	
Linoleomyristopalmitin	—	0·3	—	—	0·3	
Di-" oleo " glycerides (34·8%)						
Palmito-oleolinolein	0·2	0·9	5·0	—	6·1	
Palmitodiolein	0·3	—	23·9	4·5	28·7	
Tri-unsaturated glycerides (3·3%)						
Linoleodiolein	—	—	—	2·6	2·6	
Triolein	—	—	—	0·7	0·7	

A portion of fraction *C* on hydrogenation, followed by similar crystallisation from ether at high dilution, gave a practically quantitative yield of β-stearo-αα′-dipalmitin (m. p. 68—68·5°), indicating the presence of β-oleo-αα′-dipalmitin in this fraction, and again giving no evidence of the occurrence of the unsymmetrical isomer.

These findings are in general agreement with those of earlier work in that when one component acid in a relatively simple fat is greatly in excess of the other the resulting glycerides tend to assume the symmetrical configuration.

(b) Sapium discolor *seed from Hong Kong.* The considerable difference in the proportions of palmitic and oleic acid in this tallow as compared with that from *Sapium sebiferum* seed is reflected in the component glycerides.

Table III shows that the fat still remains remarkably simple in composition in that two major component glycerides, oleodipalmitin and palmitodiolein, between them constitute approximately 80% of the whole fat, no other component occurring to the extent of over 6%.

In *Sapium discolor* fruit-coat fat there is no evidence of the occurrence of fully saturated glycerides; no fraction of iodine value substantially lower than 31·4 (oleodipalmitin I.V. 30·5) was obtained, and it is known (Meara, *J.*, 1947, 773; 1948, 722) that it is relatively easy to separate fully saturated glycerides from dioleo-glycerides by crystallisation.

More than half of the fat is seen to consist of oleodipalmitin. Moreover, all the stearic acid occurs in mono-unsaturated glycerides (therefore as oleopalmitostearin or oleomyristostearin), none occurring in the di-unsaturated glyceride fractions, as is indicated by the absence of stearic acid from fraction *D* which contains only di- and tri-unsaturated glycerides.

Table IV compares the experimentally found component glycerides of these fats with those which can be computed from their component fatty acids by the application of the rule of even distribution, as most completely enunciated by Hilditch (*J. Amer. Oil Chem. Soc.*, 1949, **26**, 41), and by random distribution.

TABLE IV.

Observed and computed values of the component glycerides of Sapium sebiferum *and* Sapium discolor *fruit-coat fats.*

	Sapium sebiferum,			*Sapium discolor*,		
		computed,			computed,	
	observed.	even.	random.	observed.	even.	random.
Tripalmitin	8·2	13·9	28·0	—	—	11·6
Stearodipalmitin	13·1	6·3	9·1	—	—	1·4
Oleomyristopalmitin	1·8	1·8	—	4·9	6·0	2·6
Oleomyristostearin	—	—	trace	0·8	—	trace
Oleopalmitostearin	8·1	15·0	7·2	4·9	5·7	2·5
Oleodipalmitin	64·4	58·5	32·7	51·0	46·9	31·8
Linoleomyristopalmitin	—	—	trace	0·3	—	trace
Linoleodipalmitin	2·3	3·3	1·9	—	—	2·2
Palmito-oleolinolein	2·1	1·2	1·4	6·1	9·0	3·9
Palmitodiolein	—	—	12·9	28·7	32·4	28·6
Linoleodiolein	—	—	trace	2·6	—	1·7
Triolein	—	—	1·6	1·7	—	8·8
Other theoretically possible glycerides	—	—	5·2	—	—	4·9

It is seen that even with such simple fats as the *S. sebiferum* and the *S. discolor* tallow, although the component glycerides cannot be computed with as high a degree of accuracy as can be obtained in the case of some seed fats, notably *Allanblackia* fats, the maximum difference in the case of either fat is of the order of 7 units % between the observed values and those computed on the basis of even distribution. This in no way invalidates the general rule of even distribution since accordance with mathematical precision between experimental and computed values is not to be expected, the rule predicting to a greater or lesser degree of conformity the order of the amounts of the component glycerides to be expected in any given fat.

Much less accordance between observed and computed values is obtained when the latter are derived by the theory of random distribution, this being further strong support for the belief that random distribution of the fatty acids amongst the glycerol molecules plays little if any part in the synthesis of naturally occurring mixed triglycerides.

EXPERIMENTAL.

The seeds were extracted with acetone, by Mr. A. Crossley, B.Sc., to remove the hard coating of tallow in which the shells are enclosed, it being found (Crossley, private communication) that only after prolonged extraction does this solvent penetrate the shell and begin to extract the kernel oil.

Component Fatty Acids of Stillingia Tallows.—(a) Sapium sebiferum *seed from Hong Kong.* The fat (approximately 100 g.) was resolved by crystallisation, until 4 fractions (*A*—*D*) were obtained. Fraction *A* contained the bulk of the fully saturated glycerides, fraction *B* the residual amounts of fully saturated glycerides together with some mono-" oleo " glycerides, fraction *C* mainly mono-" oleo " glycerides, and fraction *D* mono-" oleo " and di-" oleo " glycerides, as adjudged from their respective iodine values.

The component fatty acids of each fraction were determined by the usual procedure adopted in these laboratories, spectrophotometric determinations being applied to fractions *C* and *D*, unsaturation in fractions *A* and *B* being taken as monoethenoid. From the data so obtained the component fatty acids of the tallow are deduced and are given in Table II.

(b) Sapium sebiferum *seed from South Texas, U.S.A.* The tallow obtained from the seeds of this specimen was saponified directly, on account of its high free acidity, and the component fatty acids determined (see Table I) after resolution of the mixed fatty acids into 2 fractions by crystallisation from ether at −30°.

TABLE V.

Extraction of Stillingia tallow.

	Wt. of seeds (g.).	Extraction.	Wt. of tallow.	%. Tallow.	Sap. equiv.	I.V.	Free acidity, %. as oleic.
Hong Kong *Sapium sebiferum*	657	1	109·1	16·6	272·2	25·1	0·8
		2	1·0	—	—	78·1	—
South Texas, U.S.A. *Sapium sebiferum*	854	1	151·0	17·9	269·5	18·6	45·8
		2	2·2	—	—	84·2	—
Hong Kong *Sapium discolor* ...	900	1	163·9	18·8	278·7	47·1	5·5
		2	21·3	—	—	120·0	—

(c) Sapium discolor *seed from Hong Kong.* The component acids of this tallow were determined after resolution of the fat into 4 fractions as in the case of Hong Kong *Sapium sebiferum*, the values obtained appearing in Table III and, together with those of various specimens of *Sapium sebiferum*, in Table I.

We thank Sir John Simonsen, F.R.S., Director of the Colonial Products Research Council, Dr. G. A. C. Herklots and Mr. I. P. Tamworth of Hong Kong, and Mr. J. Q. Wood of Oklahoma, U.S.A., for placing the materials used in this investigation at our disposal, Professor T. P. Hilditch, F.R.S., for his advice and criticism, and the Government of East Panjab (India) for a maintenance grant to one of us (S. S. G.).

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272. *N-Substituted Amino-acids. Part I. A New Method of Preparation of Dimethylamino-acids.*

By R. E. BOWMAN and (the late) H. H. STROUD.

Aliphatic and aromatic amino-acids can be converted into their *NN*-dimethyl derivatives by reductive condensation with formaldehyde and hydrogen in the presence of palladised charcoal. Aromatic nitro-acids can be reduced and *N*-methylated in one operation.

IN connection with investigations on the relative configurations of the naturally occurring amino-acids, carried out several years ago in this laboratory under the direction of Dr. F. Barrow, it became necessary to prepare the *NN*-dimethyl derivatives of some of them in an optically active form. The methods hitherto employed for the resolution of the simple amino-acids are not directly applicable to their dimethyl derivatives, but in preliminary experiments *NN*-dimethylalanine was resolved by means of its (−)-menthyl ester (Halliday, Thesis, Univ. of London, 1938), and optically pure (+)-*dimethyl-L-alanine* was isolated. This method was, however, not so successful when extended to other dimethylamino-acids, and attention was therefore directed to their preparation by the direct methylation of the unsubstituted amino-acids.*

A review of the literature revealed that, although the behaviour of a large number of amino-acids towards all the usual methylating agents had been examined, there is at present no satisfactory method available for the conversion of amino-acids into their dimethyl derivatives: methyl iodide in the presence of alkali leads to betaines, occasionally accompanied by mono- or di-alkylamino-acids; diazomethane leads to the methyl esters or mixtures thereof with the corresponding betaines; formaldehyde in the presence of formic acid has little value except for glycine and α-amino*iso*butyric acid, whose *NN*-dimethyl derivatives were obtained in satisfactory yield (Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, **1933**, **55**, 4571.

Reductive condensation of amines with aldehydes or ketones in the presence of hydrogen and a catalyst (Skita and his co-workers, *Ber.*, 1928, **61**, 1151 *et seq.*) has been frequently employed in recent years for the alkylation of amines. It has now been applied to amino-acids and peptides, furnishing a simple and convenient method for the preparation of both their mono- and their di-alkyl derivatives.

The reaction was first applied to the methylation of DL-alanine, a mixture of the amino-acid and formaldehyde being submitted to catalytic reduction in aqueous solution in the presence of palladised charcoal. Reduction proceeded readily at ordinary temperature and pressure, and *NN*-dimethyl-DL-alanine was isolated in almost quantitative yield. This method was then subsequently extended, with complete success, to glycine and the inactive forms of valine, leucine, phenylglycine, and phenylalanine.

Aromatic amino-carboxylic and amino-sulphonic acids may also be thus methylated, anthranilic and sulphanilic acids being readily converted into their dimethyl derivatives. It is of interest that the aromatic amino-acids may be replaced by the corresponding nitro-acids which are reduced and then methylated in one operation; the three isomeric dimethylaminobenzoic acids have been prepared in this manner, and the sodium salt of *p*-nitrotoluene-2-sulphonic acid has been converted into *sodium 4-dimethylaminotoluene-2-sulphonate*.

Attention was then directed to the preparation of the *NN*-dimethyl derivatives of the optically active forms of some of the naturally occurring amino-acids. Methylation at ordinary temperature was not attended with racemisation and the NN-*dimethyl* derivatives of (−)-D-alanine, (+)-L-*valine*, (+)-D-*leucine*, (−)-L-*phenylalanine*, and (−)-L-*tyrosine* were isolated in almost quantitative yields. (−)-L-Cystine gave NN-*dimethylcysteine* owing to the simultaneous reduction of the disulphide group: this dimethyl derivative very readily undergoes atmospheric oxidation to (−)-NNN′N′-*tetramethyl*-L-*cystine*.

* The major part of the work described in this paper was carried out by (the late) H. H. Stroud and forms part of a thesis submitted by him for the degree of Ph.D. (Univ. of London) in June, 1939.

(+)-L-Aspartic and (+)-L-glutamic acids have also been methylated by this method. The *NN*-dimethyl derivative of aspartic acid is noteworthy in that it is rapidly racemised in aqueous solution at 100° and differs in this respect from all the other optically active dimethylamino-acids so far examined.

Melting points and specific rotations of the active *NN*-dimethylamino-acids are given in the Table, together with the corresponding data for the unmethylated acids:

	$[\alpha]_D$ in water.	M. p.		$[\alpha]_D$ in water.	M. p. (decomp.).
(−)-*Dimethyl*-D-*alanine*	− 8·73°	188°	(−)-D-Alanine	− 2·7°	297°
(+)-*Dimethyl*-L-*valine*	+ 40·6	153	(+)-L-Valine	+ 6·4	315
(−)-*Dimethyl*-D-*leucine*	− 49·6	198	(+)-D-Leucine	+ 10·3	293
(+)-*Dimethyl*-L-*phenylalanine*	+ 77·1	218	(−)-L-Phenylalanine.....	− 35·3	283
(+)-*Dimethyl*-L-*tyrosine*	+ 74·3	300	(−)-L-Tyrosine	− 8·7 •	314
(−)-*Tetramethyl*-L-*cystine* ...	−146	106	(−)-L-Cystine	−220 •	258
(+)-*Dimethyl*-L-*aspartic acid*	+ 14·4	184	(+)-L-Aspartic acid	+ 6·0	270
(+)-*Dimethyl*-L-*glutamic acid*	+ 40·3	192	(+)-L-Glutamic acid	+ 12·6	213

• In hydrochloric acid solution.

It will be observed that the methylation is sometimes accompanied by a change in the sign of rotation, but with acids belonging to the same steric series the rotation is always displaced in the same direction. Thus, in the case of the naturally occurring amino-acids (L-series), methylation results in a displacement of the rotation in a positive direction. It is possible that this displacement might be utilised in assigning configurations to amino-acids of undetermined stereochemical structure.

The dimethyl derivatives of amino-acids show marked differences in properties from the parent compounds. Whereas the latter melt indefinitely at high temperatures with decomposition, the dimethyl derivatives (except dimethyltyrosine) melt without decomposition and generally at much lower temperatures. The dimethyl derivatives are also more readily volatile and many of them can be sublimed under diminished pressure at temperatures near their melting points. Methylation also markedly increases the solubility. In alcohol and acetone the unmethylated acids are practically insoluble but, with few exceptions, the dimethyl derivatives dissolve readily in alcohol and are also somewhat soluble in acetone. The methylated acids are also much more soluble in water; *NN*-dimethyltyrosine, for example, is over fifty times more soluble than tyrosine; dimethyl-glycine and -alanine are deliquescent.

It is noteworthy that in every case so far investigated the amino-acids have given their dimethyl derivatives; no evidence has been found of the formation of monomethyl derivatives. In the succeeding paper it is shown that alkylations effected by reductive condensation of amino-acids $R{\cdot}CH(NH_2){\cdot}CO_2H$ with homologues of formaldehyde are subject to steric influences exercised by the group R, monoalkylation being readily accomplished in the case of amino-acids which contain a branched-chain in the β- or γ-position. The possibility of preparing monomethyl derivatives, therefore, appeared to be more favourable in the case of valine and α-amino*cyclo*hexylacetic acid, which have branched chains in the β-position. However, even with these acids under conditions favourable to the formation of monomethyl derivatives, only the dimethyl derivatives and the unchanged amino-acids could be isolated.

Reductive condensation with formaldehyde may also be applied to the hydrochlorides and the esters. Thus DL-lysine hydrochloride was readily converted into *NNN'N'-tetramethyl*-DL-*lysine*; and DL-alanine hydrochloride gave its dimethyl derivative, although somewhat more slowly than the free amino-acid. Glycine ethyl ester hydrochloride was also converted into its *NN-dimethyl* derivative, provided that the methylation was carried out under anhydrous conditions, *i.e.*, in the presence of dry paraformaldehyde and anhydrous magnesium sulphate in absolute ethanol.

Experimental.

Formaldehyde employed was the commercial aqueous solution (*ca.* 40%). Polarimetric determinations were made in 2-dm. tubes.

Methylation of Amino-acids.—Unless otherwise stated, methylations were carried out by stirring a solution or suspension of the amino-acid (5 g.) in water (200 ml.) containing twice the theoretical amount of aqueous formaldehyde with palladised charcoal (5 g. of 10%) in an atmosphere of hydrogen at ordinary pressure and temperature until either reduction ceased or slightly more than the theoretical amount of hydrogen had been absorbed; with the free amino-acids the period of reduction varied from 3 to 12 hours. The mixture was then heated to boiling and filtered, and any amino-acids remaining with the catalyst extracted with hot water. Evaporation of the combined filtrates furnished the dimethylamino-acids in almost quantitative yield, together with some paraformaldehyde which was removed by re-evaporation with water.

NN-Dimethylglycine. This crystallised from ethanol–acetone in very deliquescent prisms, m. p. 176—178°; sublimation at 110—120°/0·5 mm. raised the m. p. to 182—183°, a value much higher than any previously recorded (Found: N, 13·6. Calc. for $C_4H_9O_2N$: N, 13·6%). *NN-Dimethylglycine ethyl ester hydrochloride* was prepared by methylation of glycine ester hydrochloride (14 g.) under anhydrous conditions in absolute ethanol (150 ml.) with paraformaldehyde (20 g.) in the presence of palladised charcoal (5 g. of 10%) and anhydrous magnesium sulphate (10 g.). Reduction was slow at room temperature but much more rapid at 54°, the theoretical volume of hydrogen being then absorbed in 8 hours. After filtration, the solution was evaporated to dryness. The residue slowly solidified when kept *in vacuo* over sulphuric acid and then crystallised from acetone–ether in extremely deliquescent slender needles, m. p. 88—90° (Found: Cl, 20·0. $C_6H_{13}O_2N,HCl$ requires Cl, 21·1%).

*NN-Dimethyl-*DL*-alanine*, prepared from DL-alanine, crystallised from aqueous acetone as a *monohydrate*, prisms, m. p. 182° (Found: N, 10·4. $C_5H_{11}O_2N,H_2O$ requires N, 10·4%). Evaporation of its ethanolic solution to dryness on the steam-bath, followed by crystallisation of the residue from ethanolic acetone, furnished the anhydrous amino-acid in deliquescent, colourless prisms, m. p. 185° (cf. Duvillier, *Bull. Soc. chim.*, 1892, [iii], **7**, 99) (Found: N, 12·0. Calc. for $C_5H_{11}O_2N$: N, 12·0%). The *hydrochloride* crystallised from ethanol–light petroleum (b. p. 40—60°) in hygroscopic prisms, m. p. 148° (Found: N, 9·2; Cl, 23·1. $C_5H_{11}O_2N,HCl$ requires N, 9·1; Cl, 23·1%). The *copper* salt, prepared by digesting an aqueous solution of the amino-acid with freshly precipitated copper hydroxide, separated from ethanol as the *dihydrate*, in blue, non-efflorescent prisms (Found: N, 8·5; Cu, 19·2. $(C_5H_{10}O_2N)_2Cu,2H_2O$ requires N, 8·5; Cu, 19·2%); an efflorescent heptahydrate has been described by Duvillier (*loc. cit.*).

(−)-*NN-Dimethyl-*D*-alanine.*—(−)-Benzoyl-D-alanine, prepared by the resolution of the inactive compound (Pope and Gibson, *J.*, 1912, **101**, 939), was hydrolysed with hydrochloric acid and the resulting (−)-D-alanine hydrochloride (3·8 g.), $[\alpha]_D^{15}$ −9·13° in water (*c*, 13·1), was methylated with formaldehyde (15 ml.) at ordinary temperature, the reduction being complete in 12 hours. The hydrochloride was purified as above and converted into the free *dimethylamino-acid* via the silver salt in the usual manner. Crystallised from acetone–ethanol, this formed very deliquescent prisms having m. p. 184°, $[\alpha]_D^{15.0}$ −3·5°, $[\alpha]_{5461}^{15.0}$ −4·2° (*c*, 5·10 in ethanol), and $[\alpha]_D^{17.4}$ −8·7°, $[\alpha]_{5461}^{17.4}$ −10·5° (*c*, 5·12 in water) (Found: N, 12·0. $C_5H_{11}O_2N$ requires N, 12·0%).

(+)-*NN-Dimethyl-*L*-valine*, prepared from (+)-L-valine, $[\alpha]_D^{15}$ +6·4° (*c*, 4·5 in water), crystallised from acetone–ethanol in long slender, slightly hydroscopic needles, m. p. 154°, and had $[\alpha]_D^{15}$ +34·1°, $[\alpha]_{5461}^{15}$ +40·1° (*c*, 2·02 in ethanol), and $[\alpha]_D^{15}$ +40·6°, $[\alpha]_{5461}^{15}$ +48·2° (*c*, 2·15 in water) (Found: N, 9·7. $C_7H_{15}O_2N$ requires N, 9·7%).

NN-Dimethyl-DL-valine, previously obtained by Karrer *et al.* (*Helv. Chim. Acta*, 1922, **5**, 469) as a crystalline hygroscopic mass (m. p. not stated) by interaction of dimethylamine and (±)-α-bromoisovaleric acid, was readily prepared in a pure condition by the methylation of DL-valine. It crystallised from acetone–ethanol in slightly hygroscopic prisms, m. p. 152° (Found: N, 9·6%), and formed a *hydrochloride* which separated from the same solvent in slender needles, m. p. 164° (Found: Cl, 19·5. $C_7H_{15}O_2N,HCl$ requires Cl, 19·5%); the *copper* salt crystallised as a *monohydrate* in ruby-red, rhombic prisms when its aqueous solution was evaporated at *ca.* 60° (Found: Cu, 17·3; N, 7·6; loss on drying at 100°/2 mm., 4·5. $C_{14}H_{28}O_4N_2Cu,H_2O$ requires Cu, 17·2; N, 7·6; H_2O, 4·9%). When the monohydrate remained in contact with the mother-liquor for 2 days at room temperature, it was transformed into a *dihydrate*, which crystallised in lustrous, deep-blue prisms (Found: Cu, 16·3; N, 7·2; loss on drying at 100°/2 mm., 10·6. $C_{14}H_{28}O_4N_2Cu,2H_2O$ requires Cu, 16·4; N, 7·4; H_2O, 9·3%), the anhydrous salt forms a bronze coloured powder.

(−)-*NN-Dimethyl-*D*-leucine*, prepared from (+)-D-leucine having $[\alpha]_D^{15}$ +10·3° (*c*, 2·02 in water), crystallised from ethanol–acetone in long needles, m. p. 210°, and had $[\alpha]_D^{15}$ −35·8°, $[\alpha]_{5461}^{15}$ −42·4° (*c*, 3·15 in ethanol) and $[\alpha]_D^{15}$ −49·6°, $[\alpha]_{5461}^{15}$ −58·2° (*c*, 3·15 in water) (Found: C, 60·6; H, 10·7; N, 8·7. $C_8H_{17}O_2N$ requires C, 60·3; H, 10·8; N, 8·8%).

NN-Dimethyl-DL-leucine, obtained by methylating inactive leucine, has m. p. 187—188°. A *NN*-dimethyl-leucine showing a lævorotation (value not stated) has been obtained by Karrer *et al.* (*Helv. Chim. Acta*, 1921, **4**, 76) as a hygroscopic mass, m. p. 185°, by the interaction of dimethylamine with (−)-α-bromoisohexoic acid. Since neither of the dimethyl-leucines described above is hygroscopic, Karrer's product was impure and, from its m. p., appears to have consisted mainly of the inactive form.

(+)-*NN-Dimethyl-*L*-phenylalanine*, prepared from (−)-L-phenylalanine having $[\alpha]_D^{15}$ −35·3° (*c*, 2·01 in water), separated from aqueous ethanol in needles, m. p. 218°, $[\alpha]_D^{15}$ +77·1°, $[\alpha]_{5461}^{15}$ +91·7° (*c*, 1·32 in water) (Found: N, 7·1. $C_{11}H_{15}O_2N$ requires N, 7·2%).

*NN-Dimethylphenyl-*DL*-alanine* crystallised from methanol in small prisms, m. p. 228° (Found: N, 7·2%), and furnished a *copper* salt which separated from water as a light-blue crystalline powder (Found: N, 5·9; Cu, 13·8. $C_{22}H_{28}O_4N_2Cu$ requires N, 6·3; Cu, 13·9%).

(+)-*NN-Dimethyl-*L*-tyrosine.*—The methylation of natural (−)-L-tyrosine in aqueous suspension (5 g. in 250 ml.) proceeded very slowly at ordinary temperature, but was complete in 5·5 hours at 65°. It crystallised from water in felted masses of filamentous needles, which slowly changed into short stout prisms when allowed to remain in contact with the mother-liquor. Both *forms* had the same rotation, *viz.*, $[\alpha]_D^{15}$ +74·3°, $[\alpha]_{5461}^{15}$ +89·7° (*c*, 2·07 in water), and showed a similar behaviour when heated. They became brown at *ca.* 220° and had m. p. varying from 240° to 290° (decomp.) according to the rate of heating; when rapidly heated after being plunged in a bath at 295° they both melt at 300° (decomp.) (Found: C, 63·3; H, 7·2; N, 6·6. $C_{11}H_{15}O_3N$ requires C, 63·1; H, 7·2; N, 6·7%).

(−)-L-Cystine, $[\alpha]_D^{15}$ −220° (*c*, 1·832 in N-HCl), on methylation absorbed slightly more than 5 molecular proportions of hydrogen indicating that simultaneous reduction to *NN*-dimethylcysteine had taken place. The latter was isolated as a colourless gum which could not be obtained in a crystalline condition, but after oxidative exposure to air, followed by crystallisation from acetone, it furnished (−)-*NNN'N'-tetramethyl-*L*-cystine* in needles, m. p. 105—107° after softening at 95°, $[\alpha]_D^{15}$ −121°, $[\alpha]_{5461}^{15}$ −146° (*c*, 0·50 in ethanol), $[\alpha]_D^{15}$ −146°, $[\alpha]_{5461}^{15}$ −170° (*c*, 0·543 in water) (Found: C, 40·7; H, 6·7; N, 9·6. $C_{10}H_{20}O_4N_2S_2$ requires C, 40·5; H, 6·8; N, 9·5%).

*NNN'N'-Tetramethyl-*DL*-lysine hydrochloride*, prepared from DL-lysine hydrochloride in the usual

manner, separated from acetone–ethanol in extremely hygroscopic prisms, m. p. 203—204° after prolonged drying over sulphuric acid (Found: N, 11·6. $C_{10}H_{21}O_3N_2Cl$ requires N, 11·7%).

(+)-NN-*Dimethyl-*L*-aspartic acid* was isolated from the aqueous solution resulting from the methylation of natural (+)-L-aspartic acid, by evaporation under diminished pressure below 30° in order to avoid racemisation. It crystallised from aqueous ethanol in slender prisms, m. p. 184°, $[\alpha]_D^{20}$ +14·4°, $[\alpha]_{5461}^{24}$ +17·5° (*c*, 3·06 in water) and showed no change in rotation when its aqueous solution was kept at room temperature for 13 hours; but it underwent racemisation when the solution was heated at 100°, the initial value, $[\alpha]_D^{20}$ +14·4° (*c*, 3·06), falling to +8·5°, +5·0°, and +2·3° after 2, 4, and 8 hours, respectively (Found: N, 8·7. $C_6H_{11}O_4N$ requires N, 8·7%).

NN-Dimethyl-DL-aspartic acid, previously obtained by Korner and Menozzi (*Atti R. Accad. Lincei*, 1896, [v], **I**, 457), was readily obtained by heating an aqueous solution of the active dimethylamino-acid on the steam-bath for 24 hours. It crystallised from aqueous ethanol in small prisms, m. p. 175° (Found: N, 8·6%), and formed a *hydrochloride*, prisms, m. p. 160°, from acetone–ethanol (Found: N, 7·1; Cl, 17·9. $C_6H_{11}O_4NCl$ requires *N*, 7·1; Cl, 17·9%); the *copper* salt separated as a bluish-green microcrystalline *monohydrate*, when its aqueous solution was allowed to evaporate spontaneously at ordinary temperature (Found: N, 5·5; Cu, 26·0; loss over P_2O_5 at 95°/1·5 mm., 6·8. $C_6H_9O_4NCu,H_2O$ requires N, 5·8; Cu, 26·4; H_2O, 7·5%).

(+)-*Dimethyl-*L*-glutamic acid*, prepared from the natural (+)-L-glutamic acid, crystallised from aqueous ethanol in short prisms, m. p. 192°, $[\alpha]_D^{20}$ +40·3°, $[\alpha]_{5461}^{24}$ +48·3° (*c*, 3·71 in water); these values of $[\alpha]$ were unchanged after the solution had been heated for 5 hours at 100° (Found: C, 48·1; H, 7·3; N, 7·9. $C_7H_{13}O_4N$ requires C, 48·0; H, 7·5; N, 8·0%).

Experiments on Partial Methylation.—(a) *With valine.* Methylation of the inactive acid (5·9 g.) in ethanol (100 ml.) with aqueous formaldehyde (7·5 ml.) in the presence of palladised charcoal (4 g.: 10% of Pd) was carried out at room temperature and interrupted after 2 hours when the volume of hydrogen taken up amounted to 20% above that required for monomethylation. Working up as usual and crystallisation from acetone–ethanol gave *NN*-dimethylvaline (3 g.), m. p. (and mixed m. p.) 152°. The amino-acid remaining with the catalyst was extracted with hot ethanol (30 ml.) containing concentrated hydrochloric acid (3 ml.) and then liberated by the addition of pyridine (5 ml.). It weighed 2·4 g. and consisted of unchanged valine, m. p. (and mixed m. p.) 291°.

(b) *With α-aminocyclohexylacetic acid.* The methylation of the amino-acid (1·97 g.) was carried out at 56° under the same conditions as those described for valine, and the products were isolated in a similar manner. The amino-acid (0·52 g.) insoluble in ethanol consisted of unchanged α-aminocyclohexylacetic acid, m. p. (and mixed m. p.) 297° whilst the soluble portion (1·42 g.), after crystallisation from dioxan, furnished *α-dimethylaminocyclohexylacetic acid* in rosettes of small needles, m. p. 176—177° (Found: N, 7·6. $C_{10}H_{19}O_2N$ requires N, 7·6%).

(c) *With α-aminoisobutyric acid.* After methylation at room temperature, slightly less than half of the amino-acid was recovered unchanged, m. p. 290°, the remainder being converted into *α-dimethylaminoisobutyric acid*, which crystallised from ethanol–dioxan in needles, m. p. 275° with previous partial sublimation (Found: N, 11·9. $C_4H_{11}O_2N$ requires N, 10·7%), and gave a hydrochloride, m. p. 264°, in agreement with the value given by Clarke *et al.* (*loc. cit.*).

Methylation of Aromatic Amino-acids.—The isomeric dimethylaminobenzoic acids were prepared in acetic acid, preliminary experiments with anthranilic acid having shown that the methylation could not be effected in aqueous or aqueous–ethanolic solution on account of the separation of a resinous mass consisting, presumably, of a methylene derivative, which enclosed the catalyst and prevented further reduction. In acetic acid solution (75 ml.) the reduction of anthranilic acid (7 g.) with aqueous formaldehyde (25 ml.) in the presence of palladised charcoal (2·5 g. of 10%) at room temperature was complete in 13 hours. The residue, obtained by evaporating the solution, slowly solidified and on crystallisation from ether furnished *NN*-dimethylanthranilic acid in prisms, m. p. 72° (Found: C, 65·4; H, 6·6; N, 8·6. Calc. for $C_9H_{11}O_2N$: C, 65·4; H, 6·7; N, 8·5%) (cf. Cohen and Dudley, *J.*, 1910, **97**, 1746).

The dimethylaminobenzoic acids were also prepared from the corresponding nitro-acids by simultaneous reduction and methylation in ethanolic solution. Thus, the reduction of *m*-nitrobenzoic acid (16·7 g.) in aqueous ethanol (80 ml. of 80%) in the presence of aqueous formaldehyde (50 ml.) occupied 3 hours and furnished *m*-dimethylaminobenzoic acid, m. p. 150°, in almost theoretical yield (Found: C, 65·6; H, 6·6; N, 8·5%).

In one experiment in which *p*-nitrobenzoic acid was employed, the preparation of the catalyst, the reduction of the nitro-compound, and the methylation of the resulting amino-acid were accomplished in one operation by stirring a mixture containing aqueous formaldehyde (25 ml.), ethanol (100 ml.), water (125 ml.), *p*-nitrobenzoic acid (10 g.), sodium acetate (5 g.), charcoal (5 g.), and palladium chloride (1 g. dissolved in 5 ml. of 2N-hydrochloric acid), in hydrogen at room temperature; reduction was complete in 45 minutes. After filtration and extraction of the catalyst with ethanol, the combined solutions were concentrated by evaporation until crystallisation commenced, *p*-dimethylaminobenzoic acid (8 g.) separating in needles, m. p. 240° (Found: C, 65·7; H, 6·8; N, 8·6%); previous values given for the m. p. vary from 234—243·5°.

Sulphanilic acid was also methylated in aqueous solution, and the resulting *NN*-dimethyl derivative isolated as of the monohydrate described by Bamberger and Tschirner (*Ber.*, 1899, **32**, 1892).

Sodium NN-*dimethyl-p-toluidine-2-sulphonate*, prepared by reducing the sodium salt of *p*-nitrotoluene-2-sulphonic acid in aqueous solution (11 g. in 100 ml.) containing aqueous formaldehyde (25 ml.), separated from ethanol as a *dihydrate* in the form of a white crystalline powder from which the water was not completely removed after 3 hours at 160°/2 mm. (Found: N, 5·1; Na, 8·4. $C_9H_{12}O_3NSNa,2H_2O$ requires N, 5·1; Na, 8·4%).

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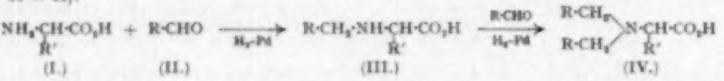
273. *N-Substituted Amino-acids. Part II. The Reductive Alkylation of Amino-acids.*

By R. E. Bowman.

The alkylation of amino-acids by reductive condensation with higher aliphatic aldehydes has been studied. With straight-chain aldehydes at room temperature glycine and alanine furnish the corresponding *NN*-dialkylamino-acids, but other amino-acids undergo monoalkylation owing to steric hindrance brought about by the group R′ (cf. III). With aldehydes branched in the α-position, all the amino-acids which have so far been examined yielded *N*-monoalkyl derivatives.

It has been shown (preceding paper) that amino-acids (I) may be converted into their *NN*-dimethyl derivatives (IV; R = H) by catalytic reduction in the presence of formaldehyde (II; R = H).

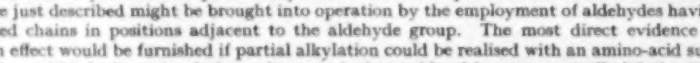


In extending this reaction to the higher aldehydes, attention was first directed to the reductive alkylation of glycine. The reduction was carried out at ordinary temperature as described previously and from acetaldehyde, propaldehyde, *n*-butanal, *n*-heptanal, and furfuraldehyde the corresponding NN-*dialkyl* derivatives were obtained. The reactions took place as readily as those with formaldehyde, but difficulties were encountered in the purification of the alkyl derivatives owing to the presence of aldehyde polymerides.

In the case of valine reductive condensation with *n*-butanal in aqueous-ethanolic solution at ordinary temperature proceeded rapidly at first but almost ceased when 1 mol. of hydrogen had been taken up, the product being the monoalkylated amino-acid, N-n-*butylvaline* (III; R = Pr^n, R′ = Pr^i). In a similar manner, by use of the appropriate aldehydes, N-n-*ethyl*-, N-n-*propyl*-, N-n-*butyl*-, N-iso*butyl*-, and N-n-*heptyl-valine* were prepared. N-n-*Butyl-leucine* (III; R = Pr^n, R′ = Bu^i) and N-n-*butylamino-α-phenylacetic acid* (III; R = Pr^n, R′ = Ph) were obtained as the sole products of the reductive butylation of leucine and amino-α-phenylacetic acid, respectively.

The amino-acids in which monoalkylation occurs have a branched chain in the β- or γ-position to the carboxyl group and it therefore seemed probable that some steric effect connected with the branched chain was inhibiting further alkylation at ordinary temperature. Under more drastic conditions, *viz.*, at higher temperatures and with more prolonged reaction, the dialkyl derivatives were slowly produced. Thus, valine on reductive alkylation with *n*-heptanal at 54° furnished NN-*di*-n-*heptylvalin*e in addition to the monoheptyl derivative. Furthermore, with amino-acids in which the group R′ is not so bulky, as in alanine, the reaction was markedly dependent on the temperature. Thus, at 11° alanine and *n*-butanal gave N-n-*butylalanine* as the main product, whilst at 50° the reaction proceeded further giving a mixture which consisted predominantly of NN-*di*-n-*butylalanine*; similar results were obtained with *n*-heptanal.

Experiments on the alkylation of glycine by means of acetaldehyde, propaldehyde, *n*-butanal, and *n*-heptanal under conditions favourable to the formation of monoalkyl derivatives failed to reveal any evidence of partial alkylation. It seemed possible that steric effects similar to those just described might be brought into operation by the employment of aldehydes having branched chains in positions adjacent to the aldehyde group. The most direct evidence of such an effect would be furnished if partial alkylation could be realised with an amino-acid such as glycine, which had previously been shown to be incapable of forming monoalkyl derivatives with straight-chain aldehydes. Indeed reductive alkylation of glycine with *iso*butanal at room temperature gave N-*monoisobutylglycine* (V) accompanied by a small quantity of the *dialkyl* derivative (VI).

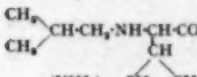


Further evidence was supplied by the reductive alkylation of glycine with 3 : 7-dimethyloctanal (VII), in which the relevant branching is in the β-position to the aldehyde group. This gave a mixture of N-3 : 7-*dimethyloctylglycine* and NN-*di*-(3 : 7-*dimethyloctyl*)*glycine* in which

the latter predominated: furthermore, *iso*butylation of alanine (I; R′ = Me) gave *N*-*isobutylalanine* as the sole product (cf. reaction with *n*-butanal).

Two further aspects of this problem have been examined with the object of obtaining additional information concerning the nature of the steric forces. First, a series of monoalkylvalines having alkyl groups of gradually increasing complexity was submitted to reductive methylation in order to discover whether the different groups exercised varying effects on the rate of further alkylation. The *N*-ethyl, *N*-*n*-propyl, *N*-*n*-butyl, *N*-*n*-heptyl, and *N*-*iso*butyl derivatives of valine did not react with hydrogen, catalyst, and formaldehyde in ethanol at room temperature, but at 54° methylation proceeded to completion in all cases in almost quantitative yield. No appreciable differences in the rates of reduction were observed.

Secondly, *N*-*iso*butylvaline (VIII), in which the steric hindrance to further alkylation would be most pronounced on account of two branched chains, was submitted to reductive alkylation in ethanol by means of acetaldehyde, propaldehyde, *n*-butanal, and *iso*butanal. As in previous cases, no reaction occurred at room temperature, but at 54°, except in the case of *iso*butanal, further alkylation proceeded to completion. No reaction took place with *iso*butanal even at 54° after prolonged reaction. It is noteworthy that these reactions allow of the preparation of a large number of "mixed" dialkylamino-acids subject only to limitations disclosed by this last example.



(VIII.)

The properties of the alkylated amino-acids are of interest in that the monoalkyl derivatives resemble the original amino-acids in having high melting points, usually with decomposition, and in being sparingly soluble in organic solvents, whereas the dialkyl derivatives melt at much lower temperatures than the parent compounds and, on the whole, are readily soluble in organic solvents. The *N*-alkyl-*N*-*iso*butylvalines in particular form low-melting waxy solids which are very readily soluble even in hydrocarbon solvents such as light petroleum.

Experimental.

The general method of reductive alkylation has already been described in Part I.

Alkylation of Glycine.—The amino-acid (0·1 mol.) was stirred in an atmosphere of hydrogen at room temperature in ethanol or aqueous ethanol (100 ml.) in the presence of the requisite aldehyde (0·4 mol.) and palladised charcoal (3 g., containing 10% of Pd) until the absorption of hydrogen ceased (0·2 mol.). After filtration from the catalyst, the solution was evaporated to dryness *in vacuo* and the resulting solid amino-acid crystallised from an appropriate solvent. The following *N*-substituted *glycines* were prepared:

	Crystalline form and solvents used.	M. p.	N, % Found.	N, % Reqd.
NN-*Diethyl*-	Slender needles,[1] benzene	131°	10·5	10·7
NN-*Dipropyl*-	Prisms,[1] acetone–light petroleum (b. p. 40—60°)	130	8·4	8·8
NN-*Di*-n-*butyl*-	Needles, benzene–light petroleum (b. p. 40—60°)	134	7·5	7·5
NN-*Di*-n-*heptyl*-	Needles, acetone	131	5·1	5·2
NN-*Difurfuryl*-	Needles, ethanol	138	5·7	5·9[2]

[1] Hygroscopic. [2] Found: C, 61·0; H, 5·7. $C_{15}H_{15}O_4N$ requires C, 61·3; H, 5·5%.

Monoalkylation of Valine, Leucine, and Phenylglycine.—A mixture of the amino-acid (0·05 mol.) and the aldehyde (0·1 mol.) was reduced at room temperature in aqueous or ethanolic solution (100 ml.) in the presence of the catalyst (2 g.) until the absorption of hydrogen almost ceased. The monoalkylamino-acids are sparingly soluble in both solvents and in the earlier experiments, which were carried out in aqueous solution, the products were separated from the catalyst by repeated extraction with boiling water. In subsequent experiments it was found more convenient to carry out the reaction in absolute ethanol and to remove the alkylamino-acids from the catalyst by extraction with hot ethanol containing slightly more than the theoretical amount of concentrated hydrochloric acid. The free amino-acids were then liberated from the ethanolic solution of their hydrochlorides by addition of the calculated amount of pyridine or aqueous ammonia. The following amino-acids were prepared in this manner:

	Crystalline form.[1]	M. p.	N, % Found.	N, % Reqd.
N-n-*Ethylvaline*	Needles	286—287°	9·4	9·7
N-n-*Propylvaline*	Plates	287—288	8·7	8·8
N-n-*Butylvaline*	Plates	269	7·8	8·1
N-iso*Butylvaline*	Oblong prisms	253—254	8·2	8·1
N-n-*Heptylvaline*	Prisms	279	6·4	6·5
N-n-*Butyl-leucine*	Plates	267	7·3	7·5
N-n-*Butyl-α-phenylglycine*	Needles	260	6·8	6·7

[1] Crystallisations were effected from boiling water.

Diheptylvaline.—The reductive heptylation was carried out in ethanol at 54° until three-quarters of the amount of hydrogen required for dialkylation had been absorbed (16 hours for 0·05 g.-mol.). Evaporation of the ethanolic filtrate furnished a yellow viscid gum from which by cooling of its solution (10%) in acetone to −50° NN-*di*-n-*heptylvaline* was obtained crystalline, m. p. 35—37° (Found: N, 4·0. $C_{19}H_{39}O_2N$ requires N, 4·5%).

Alkylation of Alanine.—(a) *With* n-*butanal at room temperature.* A mixture of alanine (4·45 g.), n-butanal (9 g.), catalyst (1·5 g.), and aqueous ethanol (100 ml. of 50%) was stirred in an atmosphere of hydrogen at 11° until 1375 ml. of gas had been absorbed (theory for monoalkylation, 1120 ml. at N.T.P.). The reaction mixture was then heated to boiling and filtered. Evaporation of the filtrate *in vacuo* furnished *N*-n-*butylalanine* as a yellow crystalline mass which, after being washed with cold acetone, separated from boiling aqueous ethanol in slender white needles, m. p. 286° (Found: N, 9·7. $C_7H_{15}O_2N$ requires N, 9·7%).

(b) *With* n-*butanal at* 54°. In this case the hydrogenation proceeded to completion and furnished the crude dialkylamino-acid as a yellow gum which solidified when kept overnight. Crystallisation from benzene–light petroleum (b. p. 40—60°) yielded NN-*di*-n-*butylalanine* in macroscopic rosettes of needles, m. p. 89° (Found: N, 6·7. $C_{11}H_{23}O_2N$ requires N, 6·9%).

(c) *With* n-*heptanal.* Reduction at room temperature furnished N-n-*heptylalanine*, needles (from water), m. p. 277° (Found: N, 7·2. $C_{10}H_{21}O_2N$ requires N, 7·5%); at 54°, NN-*diheptylalanine*, a soft waxy solid, m. p. 42—44°, b. p. 170°/0·8 mm. (Found: N, 4·6. $C_{17}H_{35}O_2N$ requires N, 4·9%), was produced.

(d) *With* iso*butanal.* The reaction was carried out at 60° as described above. The catalyst was extracted with boiling water (100 ml.), and the combined filtrates were evaporated to dryness. The residue, thus obtained, was boiled with ethanol (50 ml.); N-iso*butylalanine* remained undissolved and was purified by crystallisation from boiling water, from which it separated in slender needles, m. p. 250° (Found: N, 9·7. $C_7H_{15}O_2N$ requires N, 9·7%).

Alkylation of Glycine with Branched-chain Aldehydes.—(a) *With* iso*butanal.* A suspension of glycine (5 g.) and catalyst (3 g.) in aqueous ethanol (200 ml. of 50%) containing isobutanal (10 g.) was stirred in an atmosphere of hydrogen at 21° until 1660 ml. of gas had been absorbed (theory for monoalkylation, 1493 ml. at N.T.P.). The reaction mixture was then boiled and filtered, and the catalyst extracted with boiling water (25 ml.). The combined ethanolic and aqueous solutions were evaporated to dryness and the residue was extracted with hot ethanol (25 ml.), unchanged glycine (0·8 g.) remaining undissolved. Final evaporation of the ethanolic extract, followed by extraction with boiling benzene, furnished N-iso*butylglycine* as a crystalline solid which separated from hot ethanol in small white prisms, m. p. 203° (Found: N, 10·6. $C_6H_{13}O_2N$ requires N, 10·7%). Removal of the solvent from the benzene solution furnished a red gum which on crystallisation from hot light petroleum (b. p. 40—60°) yielded NN-*diiso*-*butylglycine* as clusters of needles, m. p. 94° (Found: N, 7·7. $C_{10}H_{21}O_2N$ requires N, 7·5%).

(b) *With* 3 : 7-*dimethyloctanal.* Citronellal (17·2 g.) was reduced to its dihydro-derivative by stirring it with palladised charcoal (4 g. of 10%) in ethanolic solution at room temperature. When the required volume of hydrogen (2420 ml.) had been absorbed, an aqueous solution of glycine (3·75 g. in 75 ml.) was introduced, and reduction continued until a further 1620 ml. had been taken up (theory for monoalkylation, 1120 ml. at N.T.P.). Fractional crystallisation, from acetone, of the residue obtained by evaporating the aqueous-ethanolic solution yielded, as a more sparingly soluble fraction, N-3 : 7-*dimethyloctylglycine* as colourless prisms, m. p. 178° (Found: N, 6·1. $C_{12}H_{25}O_2N$ requires N, 6·5%). The more soluble fraction consisted of NN-*di*-3 : 7-*dimethyloctylglycine* and crystallised in filamentous aggregates of long slender needles resembling cotton wool, m. p. 129° (Found: N, 4·2. $C_{22}H_{45}O_2N$ requires N, 3·9%).

Methylation of N-*Alkylvalines.*—A mixture of the *N*-alkylvaline (2·0 g.), catalyst (2 g.), formaldehyde (2 ml. of 40%), and absolute ethanol (100 ml.) was stirred in hydrogen at 54°, whereupon a fairly rapid absorption of hydrogen took place, the theoretical volume being taken up in 3 hours. The solution, after filtration, was evaporated to dryness and the residue re-evaporated with water until the vapours were free from formaldehyde. Final evaporation of the water furnished the *NN*-disubstituted *valines* in quantitative yield and almost pure:

*N-Methyl-*N*-alkylvalines.*

	Crystalline form and solvent.	M. p.	N, %. Found.	Reqd.
N-*Methyl*-N-*ethylvaline*	Prisms, ethanol–acetone	128°	8·8	8·8
N-*Methyl*-N-n-*propylvaline* ...	Prisms, acetone	118	8·3	8·1
N-*Methyl*-N-n-*butylvaline*	Feathery clusters, benzene–light petroleum (b. p. 40—60°)	104	7·7	7·5
N-*Methyl*-N-iso*butylvaline* ...	Plates, *cyclo*hexane–carbon tetrachloride	93	7·2	7·5
N-*Methyl*-N-n-*heptylvaline* ...	Prisms, light petroleum (b. p. 40—60°)	94	6·5	6·1

Alkylation of N-iso*Butylvaline.*—A mixture of *N*-isobutylvaline (2·6 g.), catalyst (2 g.), and the requisite aldehyde [acetaldehyde (1·5 g.), propaldehyde or n-butanal (2·5 g.)], was smoothly reduced at 54° (after failure at room temperature) in 3—4 hours. The products were worked up as in the previous

	B. p./0·6 mm.	M. p.[1]	N, %. Found.	Reqd.
N-*Ethyl*-N-iso*butylvaline*	103—106°	50—54°	6·7	6·9
N-n-*Propyl*-N-iso*butylvaline*	104—107	63—65	6·6	6·5
N-n-*Butyl*-N-iso*butylvaline*	108—110	51—54	5·9	6·1

[1] Previous softening took place about 2—4° below the m. p.

example except that final purification was effected by distillation *in vacuo*. The melting-point ranges and the waxy nature of the resulting *dialkylvalines* appear to indicate that the purification was not complete; further purification by crystallisation was impracticable on account of the extreme solubility of the products in all the common organic solvents. Attempts to force further alkylation of *N*-*iso*butylvaline by means of *iso*butanal failed.

BIRKBECK COLLEGE, LONDON, E.C.4. [*Received, February 15th,* 1950.]

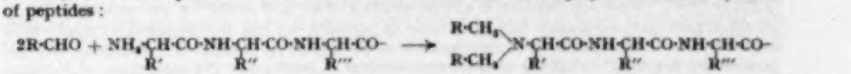
274. N-*Substituted Amino-acids. Part III. The Reductive Alkylation of Some Di- and Tri-peptides. A New Method of Determining the "End Amino-acid" in Polypeptides.*

By R. E. BOWMAN.

On reductive condensation with aliphatic aldehydes, polypeptides undergo alkylation only at the terminal amino-group. Hydrolysis of the alkylated peptide, followed by isolation of the resulting alkylamino-acid, furnishes a new method for the identification of the "end" amino-acid in a polypeptide.

PREVIOUS investigations on the alkylation of peptides have been confined to methylations by methyl iodide or diazomethane and have yielded mixtures of the corresponding betaines and their esters (Abderhalden and Kautzsch, *Z. physiol. Chem.*, 1911, **72**, 44; Imsi, *ibid.*, 1924, **136**, 192; Abderhalden and Sickel, *ibid.*, 1926, **153**, 16).

In view of the readiness with which the simple amino-acids may be converted by reductive alkylation with aliphatic aldehydes into their *NN*-dialkyl or *N*-monoalkyl derivatives (Parts I and II), it seemed probable that this method could also be employed for the alkylation of peptides:



It has already been found that hippuric acid does not undergo alkylation under the conditions usually employed and it was therefore expected that the peptide linkage would remain intact and that only the terminal primary amino-groups of the polypeptide would be alkylated; this has been found to be the case.

Thus crystalline NN-*dimethylglycylglycine*, NN-*dimethylalanylglycine*, and NN-*dimethylglycylglycylglycine* were obtained from the appropriate peptide by catalytic reduction with formaldehyde in aqueous solution at room temperature in the presence of palladised charcoal. The purification of these methylated peptides presented some difficulty since steam-distillation could not be used for removal of paraformaldehyde without risk of hydrolysis. Methylation of peptides derived from optically active amino-acids has also been accomplished. Thus glycyl-L-tyrosine has been converted into (+)-NN-*dimethylglycyl-L-tyrosine*; (+)-NN-*dimethyl-L-leucyl-L-tyrosine* and (+)-NN-*dimethyl-L-leucylglycylglycine* have also been prepared.

This methylation of the terminal amino-group paves the way for the development of a new method for the identification of the "end" amino-group in a polypeptide. A peptide (I) would give rise to the dimethyl derivative (II) which could be hydrolysed to the dimethylamino-

acid (III) and the simple amino-acids (IV) and (V). Dimethylamino-acids differ from the unmethylated acids in that they are easily soluble in ethanol and can therefore be readily separated.

In order to test these conclusions, (+)-NN-dimethylglycyl-L-tyrosine was hydrolysed with boiling hydrochloric acid and the resulting amino-acids, after isolation in the free condition *via* the silver salts, were separated by extraction with ethanol. The residue consisted of

(−)-L-tyrosine having the full activity, whilst pure *NN*-dimethylglycine was readily obtained from the ethanolic extract. In a similar manner, (+)-*NN*-dimethylglycyl-L-leucine yielded *NN*-dimethylglycine and leucine, whilst (+)-*NN*-dimethyl-L-leucylglycylglycine gave (+)-*NN*-dimethyl-L-leucine and glycine.

Attention was next directed to the alkylation of peptides by means of higher aldehydes. Although such alkylations proceed fairly readily, it was not possible, except in one case, to obtain the alkylated peptides in a crystalline condition. The products were all contaminated with aldehyde polymerides and formed viscid gums which, on prolonged storage, were transformed into hard glasses. The crude alkylated peptides were, however, submitted to hydrolysis with hydrochloric acid and, in all cases, terminal alkylation was demonstrated by the isolation of the "end" amino-acid in the form of its alkyl derivative. Thus, the products resulting from the *n*-butylation and *n*-heptylation of glycylglycine furnished *NN*-di-*n*-butylglycine and *NN*-di-*n*-heptylglycine which were readily separated from the accompanying glycine by extraction with ethanol. Similarly, the products obtained from the tripeptide, diglycylglycine, by *n*-propylation or *iso*butylation, followed by hydrolysis, were separated into *NN*-di-*n*-propylglycine and *NN*-di*iso*butylglycine, respectively, in addition to glycine itself.

It was considered of interest to extend the observations to peptides containing a terminal amino-acid such as leucine which had already been shown to furnish monoalkylderivatives. D-Leucylglycine was accordingly submitted to reductive butylation in absolute ethanol; absorption of hydrogen proceeded rapidly until the stage corresponding to monoalkylation was reached, and then ceased abruptly. Pure *N-n-butyl-D-leucylglycine* was isolated and on hydrolysis furnished, in quantitative yield, a mixture of glycine and (−)-N-n-*butyl-D-leucine* having $[\alpha]_D^{20}$ −28·7°, $[\alpha]_{5461}^{20}$ −31·7°, which were separated by taking advantage of the sparing solubility of the butyl derivative in water. Butylation of L-leucylglycylglycine gave a non-crystalline butyl derivative, which by hydrolysis furnished (+)-N-n-*butyl-L-leucine*, $[\alpha]_D^{20}$ +29·1°, $[\alpha]_{5461}^{20}$ +31·4°. Since the rotation is almost identical with that found for the optical isomer, it would appear that alkylation and hydrolysis of peptides are not accompanied by appreciable racemisation. The separation of the products of hydrolysis in the last two cases was rendered possible by the small solubility of the butyl-leucines in water, but the separation of *N*-monoalkylamino-acids from a mixture containing unsubstituted amino-acids would usually present considerable difficulties.

In view of the possibility of monoalkylation occurring and the difficulties of separation, the use of aldehydes other than formaldehyde, cannot be recommended for identifying the "end" amino-acid in a polypeptide chain; the use of formaldehyde is free from these objections.

Experimental.

Methylation of Peptides.—A solution of the peptide (2 g.) in water (100 ml.) containing aqueous formaldehyde (6 ml. of 40%) was stirred with palladised charcoal (3 g. of 10%) in an atmosphere of hydrogen at room temperature until the absorption of gas ceased. The aqueous solution was filtered, the catalyst was washed with water (20 ml.), and the combined filtrates were then evaporated to dryness under reduced pressure. The residual methylated peptide was kept *in vacuo* over sulphuric acid, in order to remove water and formaldehyde polymers as far as possible, and was then crystallised from a suitable solvent.

Hydrolysis of the methylated peptides and isolation of the resulting amino-acids were carried out as follows: the peptide was heated under reflux for 12 hours with ten times its weight of hydrochloric acid (6*N*.), and the solution, after dilution with water, was filtered and evaporated to dryness. The resulting mixture of hydrochlorides was dried over potassium hydroxide *in vacuo* and then dissolved in water (50 ml.), and the solution shaken vigorously with twice the theoretical amount of freshly precipitated silver hydroxide necessary to remove the halogen acid. After filtration, the solution was saturated with hydrogen sulphide, and the silver sulphide precipitated was removed by filtration and washed with boiling water. Evaporation of the filtrate to dryness furnished a mixture of amino-acids from which the methylated amino-acid was extracted with boiling ethanol.

Methylation of (a) *Glycyl-L-tyrosine.*—The colourless gum obtained as described above, on treatment with boiling ethanol, furnished (+)-NN-*dimethylglycyl-L-tyrosine* (1 g.) which separated from aqueous ethanol (70%) in white prisms, m. p. 159°, $[\alpha]_D^{20}$ +23·7°, $[\alpha]_{5461}^{20}$ +29·0° (*l* = 1; *c*, 3·040 in water) (Found: N, 10·2. $C_{13}H_{18}O_4N_2$ requires N, 10·5%).

The methylated peptide (0·3 g.) was hydrolysed and the resulting amino-acids were separated by extraction with boiling ethanol. The residue consisted of (−)-L-tyrosine (0·13 g.), m. p. 307—309°, $[\alpha]_D^{20}$ −8·1 (*l* = 1; *c*, 0·681 in 2% hydrochloric acid). Evaporation of the filtrate gave *NN*-dimethylglycine (0·15 g.) which, after purification by sublimation *in vacuo*, melted at 180—183°.

(b) *Glycyl-L-leucine.* Treatment of the crude reaction product with ethanolic acetone furnished *NN*-dimethylglycyl-L-leucine (0·4 g.) in slender needles, m. p. *ca.* 90°, which were very hygroscopic and rapidly liquefied on exposure to air. Extraction of the amino-acids (0·3 g.), obtained from the hydrolysis of the peptide (0·4 g.) with ethanol (10 ml.), yielded a residue consisting of leucine (0·12 g.), m. p. 269°; evaporation of the ethanolic extract yielded *NN*-dimethylglycine, m. p. 178°.

(c) L-*Leucylglycylglycine*. The colourless gum resulting from the methylation, readily crystallised from boiling ethanol and gave (+)-*NN-dimethyl*-L-*leucylglycylglycine* as colourless prisms, m. p. 172°, $[\alpha]_D^{20}$ +59·0°, $[\alpha]_{5461}^{20}$ +67·7° (*l* = 1; *c*, 3·564 in water) (Found: N, 15·5. $C_{12}H_{23}O_4N_3$ requires N, 15·4%).

A specimen of the methylated tripeptide (0·65 g.) was hydrolysed and the resulting amino-acids (0·731 g.; theory, 0·736 g.) were separated by extraction with boiling ethanol. Glycine (0·28 g.) remained undissolved, whilst (+)-*NN*-dimethyl-L-leucine was isolated from the filtrate as an extremely hygroscopic vitreous resin which, after sublimation *in vacuo* (bath, 180—190°/0·6 mm.), formed colourless crystals, $[\alpha]_D^{20}$ +30·5° (*l* = 1; *c*, 2·230 in ethanol) [cf. −35·8° in ethanol for the (−)-form; Part I].

(d) L-*Leucyl*-L-*tyrosine*. Evaporation of the combined aqueous extracts furnished (+)-*NN-dimethyl*-L-*leucyl*-L-*tyrosine* (1·45 g.) which crystallised from boiling aqueous ethanol in colourless, elongated triangular prisms, m. p. 158°, $[\alpha]_D^{20}$ +7·3°, $[\alpha]_{5461}^{20}$ +6·3° (*l* = 1; *c*, 2·856 in 0·1*N*-hydrochloric acid) (Found: N, 9·0. $C_{17}H_{26}O_4N_2$ requires N, 8·7%).

(e) *Diglycylglycine*. The crude reaction product separated from ethanolic-acetone as a white crystalline powder, m. p. 172°. *NN-Dimethyldiglycylglycylglycine* thus obtained was readily soluble in ethanol but, after remaining in a desiccator over calcium chloride for 4 years, was no longer soluble in this solvent but dissolved readily on the addition of a trace of water and then separated in clusters of colourless prisms, m. p. 172° (Found: N, 19·1. $C_8H_{13}O_4N_3$ requires N, 19·3%).

(f) *Alanylglycine*. The colourless gum, prepared according to the standard procedure, crystallised from ethanolic acetone in small white prisms (0·42 g.), m. p. 164° (Found: N, 16·7. $C_7H_{14}O_3N_2$ requires N, 16·1%).

Alkylation of Peptides with Higher Aldehydes.—Unless otherwise stated, the following general procedure was employed: A mixture of the peptide (2 g.), the aldehyde (3 mols.), catalyst (4 g.), and aqueous ethanol (100 ml. of 50%) was stirred in an atmosphere of hydrogen at room temperature until the theoretical amount of hydrogen had been absorbed. The ethanolic solution was then filtered and the catalyst washed with a further portion of the solvent. Evaporation of the combined extracts to dryness under reduced pressure furnished the alkylated peptides in the form of yellowish-brown gums. Attempts to isolate these peptides in a crystalline condition by converting them into their hydrochlorides, hydrobromides, and picrates, and also by chromatography, were unsuccessful. The crude products were therefore hydrolysed and the resulting amino-acids isolated as described for the methylated peptides.

Glycylglycine was submitted to reductive condensation with *n*-butanal and *n*-heptanal, and the mixtures of amino-acids obtained by hydrolysis were separated by extraction with hot ethanol. The residue consisted, in each case of pure glycine, m. p. 237°. Evaporation of the ethanolic extracts furnished *NN*-di-*n*-butylglycine and *NN*-di-*n*-heptylglycine, which crystallised from acetone in needles, m. p. 134° and 131°, respectively, undepressed on admixture with authentic samples.

Diglycylglycine was also alkylated by means of propaldehyde and *iso*butanal. The products were hydrolysed and then separated as in the previous experiments into glycine and *NN*-di-*n*-propylglycine [extremely hygroscopic prisms from acetone–light petroleum (b. p. 40—60°)], m. p. 130°, and *NN*-di*iso*butylglycine [needles from boiling light petroleum (b. p. 40—60°)], m. p. 92—93°, both m. p.s undepressed by authentic specimens.

Butylation of D-*Leucylglycine*.—A mixture of the peptide (1·88 g.), *n*-butanal (2·7 ml.), catalyst (2 g.), and ethanol (75 ml.) was reduced in the usual manner. The reduction proceeded very slowly at room temperature but at 50° became more rapid and finally ceased when a total of 260 ml. of hydrogen had been absorbed (theory for monoalkylation, 237 ml. at 15°). After filtration, the residue consisting of catalyst and the butylpeptide was extracted with hot ethanol (25 ml.) containing hydrochloric acid (1·5 ml. of 10*N*.). Addition of a slight excess of pyridine to the acid extract failed to precipitate the peptide which was therefore recovered from the solution by evaporation to dryness and freed from the accompanying pyridine hydrochloride by successive treatment with silver hydroxide and hydrogen sulphide as described above. Final evaporation of the resulting aqueous solution furnished *N-n-butyl*-D-*leucylglycine* (0·61 g.) as a slightly brown powder, m. p. 232° (decomp.) (Found: N, 11·4. $C_{12}H_{24}O_3N_2$ requires N, 11·5%).

Hydrolysis of the peptide (0·42 g.) gave, in almost quantitative yeild (0·455 g.), a mixture of amino-acids which by extraction with cold water (5 ml.) gave (−)-N-*n-butyl*-D-*leucine* (undissolved) as white prisms, m. p. 275°, $[\alpha]_D^{20}$ −28·7°, $[\alpha]_{5461}^{20}$ −31·7° (*l* = 1; *c*, 2·893 in 0·2*N*-hydrochloric acid) (Found: N, 7·6. $C_{10}H_{21}O_2N$ requires N, 7·5%). The aqueous solution furnished, on evaporation, glycine (0·15 g.), m. p. 235°.

Butylation of L-*Leucylglycylglycine*.—The tripeptide (1·22 g.) was stirred in hydrogen at 52° with *n*-butanal (3 ml.) and ethanol (75 ml.) in the presence of palladised charcoal (2 g.). The reaction was interrupted after 9 hours when 200 ml. of hydrogen had been absorbed (theory for dialkylation, 224 ml. at N.T.P.). The butylated peptide was isolated from the ethanol solution as a yellow gum which was hydrolysed in the usual manner. Extraction of the resulting amino-acids (0·45 g.) with boiling acetone (10 ml.), followed by crystallisation of the residue from water (2 ml.), furnished (+)N-*n-butyl*-L-*leucine* (0·11 g.) as prisms, m. p. 262°, having $[\alpha]_D^{20}$ +29·1°, $[\alpha]_{5461}^{20}$ +31·4° (*l* = 1; *c*, 2·209 in 0·2*N*-hydrochloric acid) (Found: N, 7·3. $C_{10}H_{21}O_2N$ requires N, 7·5%). The aqueous solution was evaporated to dryness and the glycine so obtained crystallised from aqueous ethanol; it had m. p. and mixed m. p. 235°.

The author of this and the preceding paper acknowledges the help and encouragement received from Dr. F. Barrow under whose direction these researches were carried out.

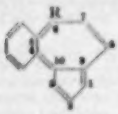
BIRKBECK COLLEGE, LONDON, E.C.4. [*Received, February 15th*, 1950.]

275. *Cyclic Conjugated Polyenes. Part IV. Attempted Synthesis of 6-Methyl-4 : 5-benzazulene.*

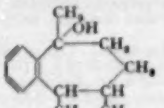
By J. R. Nunn.

An attempt to prepare 6-methyl-4 : 5-benzazulene by the dehydrogenation of 6-methyl-1 : 2 : 3 : 8 : 9 : 10-hexahydro-4 : 5-benzazulene is reported. This attempt failed but, instead, the latter hydrocarbon, on dehydrogenation, rearranged to 9-methylphenanthrene.

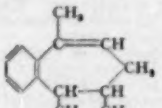
Recent attempts (Nunn and Rapson, *J.*, 1949, 1051) to isolate 4 : 5-benzazulene (I) in a pure state failed owing to instability. However, the molecular complexes of the hydrocarbon with 1 : 3 : 5-trinitrobenzene and 2 : 4 : 6-trinitrotoluene were isolated as reasonably stable compounds, presumably because of polarisation effects associated with complex formation. In an attempt to assess the factors which may control stability in the 4 : 5-benzazulene structure, an attempt has been made to prepare 6-methyl-4 : 5-benzazulene (II).



(I; R = H.)
(II; R = Me.)



(III.)



(IV.)

6-Hydroxy-6-methyloctahydro-4 : 5-benzazulene (III) was made by the action of methylmagnesium iodide on 6-keto-octahydro-4 : 5-benzazulene in the usual way, and was dehydrated to 6-*methyl*-1 : 2 : 3 : 8 : 9 : 10-*hexahydro*-4 : 5-*benzazulene* (IV) by heating it with potassium hydrogen sulphate. This was then dehydrogenated in the vapour phase in a vacuum. No conditions were found, however, under which the expected 6-methyl-4 : 5-benzazulene was produced and in all reactions the isomeric 9-methylphenanthrene was formed.

Substituted 4 : 5-benzazulenes are therefore not always accessible through dehydrogenation of hydro-derivatives, owing to the ease of rearrangement to yield derivatives of phenanthrene.

Experimental.

6-Methyl-1 : 2 : 3 : 8 : 9 : 10-*hexahydro*-4 : 5-*benzazulene* (IV).—Methylmagnesium iodide, from magnesium (0·97 g., 0·04 mol.) and methyl iodide (5·52 g., 0·039 mol.), in anhydrous ether was cooled in ice, and 6-keto-octahydro-4 : 5-benzazulene (4·0 g., 0·02 mol.) (Nunn and Rapson, *loc. cit.*) in a little anhydrous ether was added slowly with vigorous stirring. After 1 hour's refluxing the solution was set aside overnight. The complex was decomposed with ice-cold dilute sulphuric acid, and the ethereal layer was separated and washed with sodium hydrogen sulphite solution and water. Distillation of the dry neutral extract afforded 6-hydroxy-6-methyloctahydro-4 : 5-benzazulene as a colourless, very viscous oil (4·1 g., 95%), b. p. 123—125°/0·4 mm.

This carbinol (1·5 g.), mixed thoroughly with finely powdered potassium hydrogen sulphate (1·5 g.), was heated at 180—190° for 1·5 hours. The mixture was extracted with ether, and the ethereal solution washed with sodium carbonate solution (10%) and water. Distillation gave 6-*methyl*-1 : 2 : 3 : 8 : 9 : 10-*hexahydro*-4 : 5-*benzazulene* as a colourless mobile oil, b. p. 92—94°/0·3 mm., $n_D^{22\cdot0}$ 1·5769, $d_{4\cdot4}^{22\cdot0}$ 1·024, $[R]_D$ = 64·22 (Calc.: 63·00) (Found: C, 90·4; H, 9·1. $C_{12}H_{14}$ requires C, 90·9; H, 9·1%).

Dehydrogenation. The hexahydro-derivative was dehydrogenated in the vapour phase at 22 mm. over 30% palladium–charcoal, using an apparatus previously described (Nunn and Rapson, *J.*, 1949, 825). The hydrocarbon (0·80 g.) was passed through the catalyst, which was maintained at 340°, at the rate of 0·01 c.c./min. The dark distillate (0·395 g.) was dissolved in pentane (60 c.c.) and chromatographed on alumina (60 g.; Peter Spence Type H) in a column 25·5 × 1·87 cm. Fractions were collected as indicated in the table.

Fraction.	Eluent.	Eluate, c.c.	Residue, mg.	Remarks.
1—8	Pentane	420	275·9	Colourless mobile oil.
9	Pentane–benzene (9 : 1)	100	27·9	Colourless viscous oil.
10	,,	100	21·3	Colourless viscous oil.
11	Pentane–benzene (4 : 1)	100	30·9	Colourless crystals. Deep-blue fluorescence in ultra-violet light.
12	,,	100	9·6	Green oil.

Fraction 11 was again chromatographed on a column containing 5 g. of alumina with pentane only as the eluent. This afforded 24 mg. of crystalline material which, after 2 crystallisations from methanol, gave colourless prisms. These were sublimed at 85° (block temp.) at 0·01 mm. and then had m. p. 90—91° (Found: C, 93·7; H, 6·7. Calc. for $C_{13}H_{12}$: C, 93·7; H, 6·3%). The picrate formed orange-yellow needles, m. p. 151—153°, from methanol. Windaus, Jensen, and Schramme (*Ber.*, 1924, **57**, 1875) give m. p. 91—92° for 9-methylphenanthrene and m. p. 152—153° for the picrate.

Fractions 1—8 proved to be mainly unchanged starting material. Further dehydrogenations were carried out at 270°, 290°, 310°, and 360° without any of the desired product being obtained.

The author thanks Dr. W. S. Rapson for advice during this work and the South African Council for Scientific and Industrial Research for permission to publish this paper.

NATIONAL CHEMICAL RESEARCH LABORATORY,
PRETORIA, SOUTH AFRICA. [*Received, February 28th*, 1950.]

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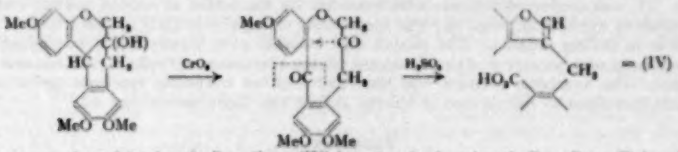
276. *A Synthesis of β-Anhydrotrimethylbrazilone.*

By K. W. BENTLEY and SIR ROBERT ROBINSON.

β-Anhydrotrimethylbrazilone is obtainable from *O*-trimethylbrazilin in three stages which involve a series of molecular rearrangements such that the product bears no obvious relation to the starting point. This α-naphthol derivative has been synthesised from an appropriately substituted *o*-hydroxydeoxybenzoin by conversion into a related phenoxyacetic acid and then ring-closure to a substituted coumaronecarboxylic acid bearing a metathetic relation to φ-trimethylbrazilone. Conversion into the acid chloride and ring-closure by Kipping's method afforded β-anhydrotrimethylbrazilone.

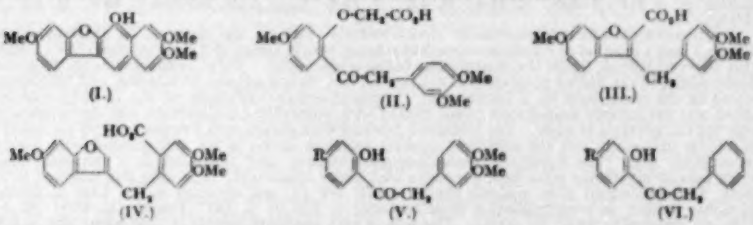
THE formation of trimethylbrazilone in the oxidation of trimethylbrazilin by chromic acid was discovered by Gilbody and Perkin in 1899 (*Proc. Chem. Soc.*, **15**, 27; cf. *idem*, *J.*, 1902, **81**, 1040). Among its remarkable transformations is the change to φ-trimethylbrazilone (IV) brought about by dissolution in concentrated sulphuric acid. This was first observed by Herzig, Pollak, and Galitzenstein (*Ber.*, 1904, **37**, 631) and elucidated by Perkin and Robinson (*J.*, 1909, **95**, 381). The annexed scheme illustrates the course of the rearrangement.



The conversion of φ-trimethylbrazilone (IV) into β-anhydrotrimethylbrazilone (I) involves a swing-round of the lower part of the molecule and elimination of the elements of water between the carboxyl group and hydrogen in the furan ring.

In order to synthesise (I) we proposed to dehydrate the acid (III) which should be obtainable from (II). This scheme was eventually realised but the methods found to be necessary to effect these ring-closures were different from those which were contemplated at the outset.

The intermediate for (II) is the ketone (V) which was obtained in only moderate overall yield. Hence the analogous series starting with (VI) was first investigated.



The preparation of 2-hydroxy-4-methoxyphenyl benzyl ketone (VI; R = OMe) by the Hoesch condensation of resorcinol and phenylacetonitrile to give 2 : 4-dihydroxyphenyl benzyl ketone (VI; R = OH) (Chapman and Stephen, *J.*, 1923, 406), followed by partial methylation of this product in alcoholic solution (Tambor, *Ber.*, 1910, **43**, 1884), gave very poor overall yields (7—10%), and much better results were obtained by the condensation of phenylacetyl chloride with 1 : 3-dimethoxybenzene in carbon disulphide solution in the presence of anhydrous aluminium chloride.

The condensation of (VI; R = OMe) with ethyl bromoacetate was very difficult to effect but was finally successfully carried out in boiling ethanol in the presence of sodium ethoxide. The resulting 5-methoxy-2-phenylacetylphenoxyacetic acid gave an intractable tar on being heated with sodium acetate and acetic anhydride under reflux for 3—4 hours, but 6-methoxy-3-benzylcoumarilic acid was produced on heating it with phosphoric anhydride in boiling benzene for an hour, a reaction which was never subsequently reproduced. Better yields were, however, consistently obtained when the ring-closure was effected by means of sodium ethoxide in boiling ethanol. Several attempts to convert this compound into 6-hydroxy-3-methoxy-β-brazan gave either polymerised compounds, which nevertheless gave the colour reactions expected for this compound from analogy (cf. Lustgarten, *Monatsh.*, 1882, **3**, 720; Perkin and Robinson, *loc. cit.*, p. 391), or gave no indication of reaction. Among the methods tried were heating with phosphoric anhydride in xylene, and heating with sodium acetate and acetic anhydride at 250° for 50 hours, followed by conversion into the acid chloride and treatment of this with aluminium chloride.

The synthesis of β-anhydrotrimethylbrazilone itself proceeded better than did the analogous reactions in the model series.

The hydroxy-ketone (V; R = OMe) was prepared in the two ways indicated for the preparation of (VI; R = OMe): first, by the partial methylation of 2 : 4-dihydroxyphenyl 3′ : 4′-dimethoxybenzyl ketone (V; R = OH), prepared by the condensation of 3 : 4-dimethoxyphenylacetonitrile and resorcinol, and, secondly, by the condensation of 3 : 4-dimethoxyphenylacetyl chloride with 1 : 3-dimethoxybenzene in boiling benzene solution in presence of anhydrous aluminium chloride. Again the second method gave the better yields.

Conversion of (V; R = OMe) into the phenoxyacetic acid derivative (II) by condensation with ethyl bromoacetate in the presence of sodium ethoxide followed the optimum conditions worked out for the preparation of 5-methoxy-2-phenylacetylphenoxyacetic acid. As with the latter, (II) was converted into an intractable tar by the action of sodium acetate and acetic anhydride at the boiling point, but was successfully changed into (III) by the action of sodium ethoxide in boiling ethanol. The related acid chloride gave β-anhydrotrimethylbrazilone (I) on treatment with an excess of powdered anhydrous aluminium chloride in cold benzene during 5 hours. The synthetic product was identified with an authentic specimen prepared from trimethylbrazilone by the method of Herzig, Pollak, and Galitzenstein (*loc. cit.*).

Experimental.

2-Hydroxy-4-methoxyphenyl Benzyl Ketone (VI; R = OMe).—Powdered anhydrous aluminium chloride (44 g.) was added to a mixture of 1 : 3-dimethoxybenzene (46 g.) and carbon disulphide (50 c.c.) slowly, with constant shaking and ice-cooling. Phenylacetyl chloride (51 g.) in carbon disulphide (50 c.c.) was then slowly added, and the mixture heated at the b. p. until evolution of hydrogen chloride ceased (about 1 hour). The excess of carbon disulphide was removed, and the hard purple aluminium complex decomposed by ice-water and hydrochloric acid. The product was isolated by means of ether, freed from acids, and crystallised from ethanol (40 g.; m. p. 90°). After one recrystallisation the m. p. was 92°, or 91° with a specimen m. p. 90° prepared by the method of Tambor (*Ber.*, 1910, **43**, 1884).

The 2 : 4-*dinitrophenylhydrazone* separated from chloroform–light petroleum in short, deep-red needles, m. p. 212° (Found: C, 59·4; H, 4·3; N, 13·5. $C_{21}H_{18}O_6N_4$ requires C, 59·7; H, 4·3; N, 13·3%).

5-Methoxy-2-phenylacetylphenoxyacetic Acid.—Sodium (4·38 g.) was dissolved in absolute ethanol (100 c.c.), and a solution of 2-hydroxy-4-methoxyphenyl benzyl ketone (9·2 g.) in ethanol (75 c.c.) added with vigorous stirring whilst the mixture was boiled under reflux. Ethyl bromoacetate (31·75 g.) was slowly added to the boiling suspension of the sodium salt, during approx. 15 minutes, and the mixture heated on the steam-bath for a further hour. Aqueous sodium hydroxide (50 c.c. of 25%) was then added, and the mixture heated for 2 hours, diluted with water (750 c.c.), acidified, and thrice extracted with 150-c.c. portions of ether. The combined extracts were shaken with five portions (25 c.c. each) of 2N-sodium carbonate, and the combined aqueous solutions cooled in ice and acidified with ice-cold hydrochloric acid. The *5-methoxy-2-phenylacetylphenoxyacetic acid* separated as a semi-solid mass, which became crystalline when kept overnight with dilute acetic acid. The solid was collected at the pump, and crystallised from aqueous alcohol (yield, 5·2 g.), and obtained in the form of slender, colourless needles on recrystallisation from benzene; it had m. p. 130° (Found: C, 67·8; H, 5·2. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%). The acid is very sparingly soluble in cold water and in light petroleum, sparingly soluble in hot water, and readily soluble in ethanol, chloroform, or acetone. Its solution in concentrated sulphuric acid exhibited a dark green fluorescence.

6-Methoxy-3-benzylcoumarilic Acid.—(*a*) 5-Methoxy-2-phenylacetylphenoxyacetic acid (1 g.) was added to a suspension of phosphoric anhydride (5 g.) in boiling benzene (50 c.c.), and the mixture refluxed for an hour and then filtered hot, and the benzene removed by distillation. The residue was crystallised from benzene, *6-methoxy-3-benzylcoumarilic acid* being obtained as long, slender, colourless needles, m. p. 190°, almost insoluble in water, light petroleum, or cold benzene, readily soluble in ethanol, acetone, or hot benzene. Its solution in cold, concentrated sulphuric acid exhibited an intense emerald-green fluorescence; when this solution was kept, the fluorescence became dark green and less intense, and

dilution no longer precipitated the acid (Found: C, 72·0; H, 4·9. $C_{11}H_{12}O_3$ requires C, 72·3; H, 5·0%).

On evaporation of the mother-liquors from the recrystallisation of this compound a small quantity of a non-crystalline solid was obtained. This was soluble in alkali, and this solution when warmed to 60° with chloroform developed a green colour, indicating the presence of 6-hydroxy-3-methoxy-β-brazan.

(*b*) Sodium (1·9 g.) was dissolved in ethanol (80 c.c.), and 5-methoxy-2-phenylacetylphenoxyacetic acid (5 g.) added. The mixture was heated under reflux for an hour, diluted with cold water, and acidified with dilute hydrochloric acid. The bulky white mass which separated was dried and crystallised from benzene (yield, 4 g.); the acid had m. p. 190°, alone or mixed with the above product.

Attempted Preparations of 6-Hydroxy-3-methoxy-β-brazan.—(*a*) 6-Methoxy-3-benzylcoumarilic acid was treated with phosphoric anhydride in refluxing xylene. The product was a greenish-yellow semi-solid mass which could not be crystallised. On being warmed with chloroform and alkali, the mixture developed a green colour, and on treatment with alkali and benzenediazonium chloride a deep red colour developed. These reactions indicated the presence of the required compound.

(*b*) 6-Methoxy-3-benzylcoumarilic acid was converted into the acid chloride by warming it with pure thionyl chloride, and anhydrous aluminium chloride was added to a solution of the acid chloride in carbon disulphide. The mixture was heated until evolution of hydrogen chloride ceased, and the hard black aluminium complex was decomposed by ice-water and hydrochloric acid, yielding a dark brown amorphous solid, which could not be obtained crystalline and showed no signs of melting below 320°. The solid was soluble in alkali, and gave both the above-mentioned colour reactions.

(*c*) 6-Methoxy-3-benzylcoumarilic acid was recovered unchanged after being heated for 52 hours at 240° in a sealed tube with acetic anhydride and fused sodium acetate, and after being heated with phosphoric anhydride and syrupy phosphoric acid for 8 hours.

2 : 4-*Dihydroxyphenyl* 3′ : 4′-*Dimethoxybenzyl Ketone* (V; R = OH).—Hydrogen chloride was passed through a mixture of 3 : 4-dimethoxyphenylacetonitrile (10 g.), resorcinol (10 g.), and powdered anhydrous zinc chloride (8 g.) in dry ether (250 c.c.) for 2 hours. The ketimine hydrochloride crystallised overnight as a mass of small, pale pink needles; it was hydrolysed by boiling it with 2N-hydrochloric acid (200 c.c.) for 2 hours. The *ketone*, a bulky, pale pink solid, was collected and crystallised from ethanol, being obtained as short, stout, colourless prisms, m. p. 176·5°. It is readily soluble in ether, benzene, acetone, or hot ethanol. The ferric reaction in alcoholic solution was a deep reddish-violet coloration (Found: C, 66·4; H, 5·3. $C_{17}H_{18}O_5$ requires C, 66·6; H, 5·5%).

The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in bright red needles, which became chocolate-brown on drying; m. p. 229° (Found: C, 58·2; H, 4·5; N, 11·4. $C_{29}H_{28}O_9N_4$ requires C, 58·4; H, 4·3; N, 11·9%).

2-*Hydroxy-4-methoxyphenyl* 3′ : 4′-*Dimethoxybenzyl Ketone* (V; R = OMe).—(*a*) Methyl sulphate (5·95 c.c., 7·82 g.) was slowly added to a well-stirred solution of 2 : 4-dihydroxyphenyl 3′ : 4′-dimethoxybenzyl ketone (6·2 g., 1 mole) in alcoholic sodium hydroxide (24·8 c.c. of 10%) and the mixture then heated for an hour, cooled, and poured into water (150 c.c.). The solid was crystallised twice from ethanol (yield, 2 g.) and obtained as bunches of very long, slender, colourless needles, m. p. 119° (Found: C, 67·9; H, 6·1. $C_{18}H_{20}O_5$ requires C, 67·6; H, 5·9%).

2-*Hydroxy-4-methoxyphenyl* 3′ : 4′-*dimethoxybenzyl ketone* is sparingly soluble in water, light petroleum, or cold ethanol, readily soluble in benzene, acetone, or hot ethanol. The alcoholic solution developed a deep violet-red colour on addition of ferric chloride.

The 2 : 4-*dinitrophenylhydrazone* crystallised from benzene in long, slender, orange needles, m. p. 198° (Found: C, 57·1; H, 4·4; N, 11·5. $C_{30}H_{30}O_9N_4$ requires C, 57·2; H, 4·6; N, 11·6%).

(*b*) Phosphorus pentachloride (13·5 g.) was slowly added to a suspension of homoveratric acid (12·5 g.) in dry benzene (40 c.c.), with exclusion of moisture. The solution was heated for 5 minutes on a steam-bath and then slowly added to a mixture of 1 : 3-dimethoxybenzene (8·8 g.) and powdered anhydrous aluminium chloride (8·5 g.) in boiling benzene (40 c.c.). The mixture was refluxed until evolution of hydrogen chloride ceased (about 1 hour). After decomposition by ice and hydrochloric acid, the benzene layer was removed, washed with dilute sodium carbonate solution and with water, dried, and evaporated. The residue after removal of the solvent was crystallised from ethanol (yield, 10 g.); m. p. 119°, alone or mixed with the product obtained as in (*a*).

5-*Methoxy*-2-(3 : 4-*dimethoxyphenylacetyl*)*phenoxyacetic Acid* (II).—2-Hydroxy-4-methoxyphenyl 3′ : 4′-dimethoxybenzyl ketone (5 g.) in ethanol (75 c.c.) was added to a solution of sodium ethoxide (1·52 g. of sodium in 150 c.c. of ethanol) with constant stirring. Ethyl bromoacetate (11·0 g.) was added to the boiling mixture, during approx. 15 minutes, and the solution refluxed for a further hour. Aqueous sodium hydroxide (50 c.c. of 20%) was added and the mixture boiled for 2 hours, and then cooled, added to water (75 c.c.), acidified with hydrochloric acid, and thrice extracted with ether. The combined extracts were shaken with five portions (20 c.c. each) of 2N-sodium carbonate solution, and the combined aqueous solutions were acidified with ice-cold hydrochloric acid. The semi-solid mass became crystalline on trituration with dilute acetic acid. The solid *acid* was collected and crystallised from glacial acetic acid (yield, 2·5 g.), being obtained as bunches of short, colourless needles, m. p. 142°, sparingly soluble in water, light petroleum, or benzene, readily soluble in ethanol, ethyl acetate, or warm glacial acetic acid (Found: C, 63·2; H, 5·6. $C_{19}H_{20}O_7$ requires C, 63·3; H, 5·6%).

6-*Methoxy*-3-(3 : 4-*dimethoxybenzyl*)*coumarilic Acid* (III).—Sodium (0·5 g.) was dissolved in ethanol (20 c.c.), and 5-methoxy-2-(3 : 4-dimethoxyphenylacetyl)phenoxyacetic acid (2 g.) added. The mixture was refluxed for 15 minutes, kept overnight, then diluted with water (100 c.c.) and acidified with hydrochloric acid. The bulky white solid was collected, washed with water, and crystallised from glacial acetic acid. The *coumarilic acid* was obtained as short, slender, colourless needles, m. p. 196·5°, sparingly soluble in water, light petroleum, benzene, or cold ethanol (Found: C, 66·3; H, 5·7. $C_{19}H_{18}O_6$ requires C, 66·6; H, 5·3%).

β-*Anhydrotrimethylbrazilone* (I).—Phosphorus pentachloride (0·8 g.) was slowly added to a suspension of 6-methoxy-3-(3′ : 4′-dimethoxybenzyl)coumarilic acid (1·2 g.) in benzene (35 c.c.), and the mixture

was heated to boiling for 10 minutes on a steam-bath. After the mixture had cooled, powdered anhydrous aluminium chloride (1 g.) was introduced and the whole kept in the cold for 5 hours. The bright red aluminium complex was decomposed by ice-water, and the solid collected and crystallised from a large volume of ethanol. The minute, very pale pink prisms so obtained had m. p. 220°, alone or mixed with an authentic specimen of β-anhydrotrimethylbrazilone. A comparison of the characteristic colour reactions of the two specimens confirmed their identity.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, March 1st*, 1950.]

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277. *The Relation between Chlorine Oxide* (ClO) *and Dichlorine Hexoxide.*

By ZOLTÁN G. SZABÓ.

Examination of the properties of, and rôles played by, the radical chlorine oxide (ClO) and dichlorine hexoxide (Cl_2O_6) shows these substances to be closely related, as indicated by the reactions

$$ClO + O_2 \rightleftharpoons ClO_3 \ (\sim 0 \text{ kcals.}) \rightleftharpoons \tfrac{1}{2}Cl_2O_6 \ (+ 850 \text{ cals.}).$$

ONLY partial success has resulted from the extensive investigations of the photochemical and thermal decomposition of dichlorine monoxide (chlorine monoxide; Cl_2O) and chlorine dioxide (ClO_2), or of the catalysed and chlorine-sensitised decomposition of ozone. These investigations have, however, established some close relations between the reactions of these substances and demonstrated that the mechanisms of the reactions of chlorine–oxygen compounds are based on common, fundamental, and simple processes. Discussion of chlorine oxide (ClO) and dichlorine hexoxide (Cl_2O_6) from this generalised viewpoint shows a close relation between them and eliminates many discrepancies inherent in the older mechanisms.

The Radical ClO.—The existence of a radical ClO was postulated in the early work and many of its properties were determined. Chlorine oxide (ClO) is produced in the reaction of dichlorine monoxide with chlorine atoms (Finkelnburg, Schumacher, and Stieger, *Z. physikal. Chem.*, **1932**, *B*, **15**, 127):

$$Cl + Cl_2O = ClO + Cl_2 + 14 \text{ kcals.}$$

and in that of chlorine dioxide and oxygen atoms (data recalculated from those of Finkelnburg):

$$O + ClO_2 = ClO + O_2 + 48 \text{ kcals.}$$

Both reactions proceed without inhibition and play an important part in the chains formed during decomposition of these gases. Thus ozone and chlorine atoms produce ClO, also without any great activation energy, as follows, the thermal value being that recalculated by use of $ClO = Cl + O - 50$ kcals. (Finkelnburg *et al.*, *loc. cit.*) from Goodeve and Marsh's data (*J.*, **1939**, **1332**):

$$Cl + O_3 = ClO + O_2 + 25{\cdot}5 \text{ kcals.}$$

Photochemical dissociation of dichlorine monoxide also affords ClO: the first maximum (at 6250 A.) in the spectrum of dichlorine monoxide corresponds to an energy of 45·5 kcals./mole, whilst the reaction $Cl_2O \longrightarrow ClO + Cl$ is endothermic to the extent of 43 kcals./mole (Finkelnburg *et al.*, *loc. cit.*).

In the decomposition of chlorine dioxide the primary reaction (occurring on the wall of the vessel) which is capable of propagating chains is, according to Schumacher and Stieger (*Z. physikal. Chem.*, **1930**, *B*, **7**, 363):

$$ClO_2 = ClO + O - 70 \text{ kcals.}$$

Experiment shows that ClO is perhaps a little more inert but nevertheless constitutes the most important propagator of these chains. Its low activity, compared with the chlorine atom, is to be ascribed to the activation energy necessary for its reactions with molecules. Its decomposition thus requires activation energy and produces a notable heat of reaction (Finkelnburg *et al.*, *loc. cit.*):

$$2ClO = Cl_2 + O_2 + 74 \text{ kcals.}$$

or, when activation is successful:

$$2ClO = 2Cl + O_2 + 17 \text{ kcals.}$$

In the latter case there is no breach of the chain but, instead, two ClO radicals which disappear produce two chlorine atoms which maintain a steady concentration of chain propagators, as Beaver and Stieger (*Z. physikal. Chem.*, **1931**, *B*, **12**, 93) found for the decomposition of dichlorine monoxide.

In the decomposition of dichlorine monoxide and chlorine dioxide, ClO doubtless plays an important rôle. However, its effect on the chlorine-sensitised or catalysed decomposition of ozone was for long unexplained, so that many discrepancies observed in these reactions have been ascribed to ClO (Hamann and Schumacher, *ibid.*, **1932**, *B*, **17**, 293). Attempts to make ClO responsible for these anomalies failed, however, since similar anomalous behaviour was not observed in other processes although ClO occurs in every reaction of chlorine–oxygen compounds. The anomalies, in fact, are due to the chlorine atoms.

The first mechanism suggested for the chlorine-catalysed decomposition of ozone was that of Bodenstein, Padelt, and Schumacher (*ibid.*, **1929**, *B*, **5**, 209), who suggested that the chains are propagated by the reaction

$$ClO_3 + O_3 = ClO_2 + O_2$$

This appeared to be supported by the formation of dichlorine hexoxide from chlorine and ozone or, better, from chlorine dioxide and ozone at low temperatures. The latter is the most convenient method of preparing dichlorine hexoxide (Schumacher and Stieger, *Z. anorg. Chem.*, **1929**, **184**, 272). It was assumed by Bodenstein and his collaborators (*ibid.*, **1925**, **147**, 233; *Z. physikal. Chem.*, **1929**, *B*, **5**, 233) that dichlorine hexoxide was formed by a readily occurring dimerisation; this was investigated in detail by Goodeve and his collaborators (*Trans. Faraday Soc.*, **1936**, **32**, 790) by measurement of magnetic susceptibilities, who found the dissociation energy $Cl_2O_6 = 2ClO_3$ to be -1700 ± 500 cals. The next step in Bodenstein's scheme was continuation of the chain, thus:

$$ClO_3 + O_3 = ClO_2 + 2O_2$$

and the chain ends by the reaction

$$2ClO_3 = Cl_2 + 3O_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (A)$$

This suggestion, that ClO_3 is a chain propagator, was accepted also by later authors, albeit more or less modified (Allmand and Spinks, *J.*, **1932**, 599; Byrns and Rollefson, *J. Amer. Chem. Soc.*, **1934**, **56**, 364, 2245), but Norrish and Neville (*J.*, **1934**, 1864) rejected it and proposed instead a chain mechanism involving ClO. From the viewpoint of reaction kinetics Byrns and Rollefson's most important result was that two forms of chlorine trioxide molecules exist, differing in reactivity, and this concept will be included in our later discussion of reactions which occur by way of ClO_3 or Cl_2O_6.

Although dichlorine hexoxide is found in traces in this and other reactions, its formation is not sufficient proof that it is an intermediate product. The most important arguments against this are the following. (*a*) All the reactions occur at high temperatures, at which the stability of ClO_3 is very doubtful. (*b*) Hamann and Schumacher (*loc. cit.*) were unable to identify any of the intermediates which should have been found spectroscopically—ClO_3 has a large absorption and should have been thus found. (*c*) Dichlorine hexoxide is stable in the liquid state, so that chain termination in Bodenstein's scheme must occur according to equation (*A*) above. This equation cannot, however, possibly represent the reaction, for it would demand the fourth order for the reverse reaction which must occur according to the principle of microscopic reversibility (Bodenstein, "Handbuch der Katalyse," Springer Verlag, Vienna, 1941, Vol. I, p. 315). (*d*) Byrns and Rollefson's assumption of an energetically distinguished molecule ClO_3^* refers, as mentioned above, not to a simple activation in the gas-kinetic sense, but to a catalytic reaction with an equally catalysed reverse reaction which deactivates the molecule; to distinguish thus between identical molecules appears a little forced.

On the other hand, in experiments in which the reaction mixture was frozen and later warmed again (Beaver and Stieger; Schumacher and Stieger; Bodenstein, Padelt, and Schumacher, *locc. cit.*) the induction period which could be very accurately measured at the beginning of the experiment was either absent or present only to a very small extent. To explain this phenomenon we must assume the presence of a more stable intermediate than the ClO radical, Cl, or O.

Chlorine dioxide can be shown to be present in each of the reactions. It also is an intermediate which could be frozen out. However, it can on no account be the intermediate discussed above, for there is an induction period in its own decomposition.

Some other intermediate must exist and, since the same behaviour is observed in all the

reactions, it must be common to them all. As this was already suggested by Norrish and Neville for the special case of ozone (*loc. cit.*), every reaction scheme embodying ClO_3 as intermediate can be written with ClO instead. Thus the reactions proceed by way of ClO and of ClO_3 or Cl_2O_6 only at low temperatures, the appropriate equation being

$$ClO + O_2 \rightleftharpoons ClO_3 \rightleftharpoons \tfrac{1}{2}Cl_2O_6$$

Since ClO occurs in all reactions of chlorine–oxygen compounds, the common intermediate which can be frozen can be no other than ClO or Cl_2O_6.

Freezing the various reaction mixtures gave different amounts of dichlorine hexoxide. This is explicable on the assumption of different concentrations of ClO in the different reaction mixtures. The concentration is notably smaller in the decomposition of dichlorine monoxide or chlorine dioxide than in the reaction of ozone with chlorine or of dichlorine monoxide. The yield of dichlorine hexoxide is also limited by the fact that its formation from ClO and oxygen ceases when the ClO is consumed as no more ClO can be formed at the low temperature of the frozen mixture. On the other hand, in the production of dichlorine hexoxide from ozone and chlorine or from chlorine dioxide the reactions leading to ClO are all primary reactions which occur at low temperature and thus uninterruptedly supply ClO.

The existence of such intermediates which can be frozen out is evidence of the reaction $ClO + O_2 \rightleftharpoons ClO_3$. However, there are also other facts which strongly support this view, particularly the properties of dichlorine hexoxide and ClO_3 (Goodeve and Richardson, *J.*, 1937, 294).

Dichlorine Hexoxide.—Dichlorine hexoxide is a dark red liquid; its freezing point (3·50° ± 0·05°) can be considerably lowered by presence of impurities and decomposition products. The liquid has strong absorption throughout the region from *ca.* 6000 A. to the limit 2000 A. The absorption of the gaseous oxide is continuous, with two maxima, one at 2780 A. and the other beginning at 2170 A. The continuous nature of the spectrum of the gas indicates that the molecule dissociates with absorption of a light quantum. We showed above that the heat of dissociation of the hexoxide to the trioxide is *ca.* 1·5 kcals., so that equilibrium in the gaseous state lies entirely on the side of ClO_3.

The second and more interesting dissociation, $ClO_3 \rightleftharpoons ClO + O_2$, is almost thermoneutral, as is readily seen from the equations,

$$2ClO = Cl_2 + O_2 + 74 \text{ kcals.}$$
$$2ClO_3 = Cl_2 + 3O_2 + (74 \pm 4) \text{ kcals.}$$

The former heat of reaction was calculated by Finkelnburg, Schumacher, and Stieger (*loc. cit.*); the latter was measured calorimetrically by Goodeve and Marsh (*loc. cit.*). These values surely contain an experimental error, but this is certainly not large enough to remove the reaction $ClO_3 \rightleftharpoons ClO + O_2$ far from thermoneutrality. Thus no great obstacle exists to the building up of ClO and ClO_3 concentrations.

The reactions of dichlorine hexoxide have not been thoroughly studied. Doubtless it reacts with ozone. Byrns and Rollefson found that the reaction is inhibited by foreign gases which deactivate the energy-rich molecules capable of propagating the chain. On the other hand, Norrish and Neville observed inhibition only by chlorine and oxygen. We showed above that the mechanism of chlorine-catalysed decomposition of ozone can be postulated with ClO instead of ClO_3. It is clear that Byrns and Rollefson's activated molecule ClO_3^* can be replaced by ClO. Norrish and Neville interpreted the inhibiting action of chlorine and oxygen as follows, on the assumption that the chlorine atom was a chain propagator:

$$Cl + O_2 = ClO_2 \qquad ClO_2 + O_2 = ClO_3 + O_2$$
and
$$Cl + Cl_2 = Cl_3 \qquad Cl_3 + O_2 = ClO_2 + Cl_2$$

Thus ClO_3 was formed and this broke the chain.

On the basis of the views reported above, the inhibiting action of oxygen and chlorine cannot be of the same nature. In Hamann and Schumacher's experiments chlorine caused inhibition where oxygen was totally without effect. This can be explained in the sense that in these experiments at higher temperatures (35—50°) the equilibrium $ClO + O_2 \rightleftharpoons ClO_3$ was shifted entirely to the left, so that the reactivity of ClO was retained whilst inhibition by chlorine occurred. Meanwhile it cannot be decided whether this inhibition by chlorine—on the assumption that chlorine dioxide is also a chain propagator—occurs by the reaction $Cl + ClO_2 = Cl_2 + O_2$ or by the reactions envisaged by Norrish and Neville utilising Cl_3.

Byrns and Rollefson (*loc. cit.*) and Goodeve and Richardson (*loc. cit.* and *Trans. Faraday Soc.*, **1937, 33, 354**) found the activation energy for the decomposition of dichlorine hexoxide to be *ca.* 22 kcals. Bodenstein and his collaborators calculated a heat of activation of 11—22 kcals. for the reaction $2ClO_3 = Cl_2 + 3O_2$. Clearly the latter value represents the activation energy of the reaction $2ClO = Cl_2 + O_2$ in the experimental conditions used by these authors. The discrepancy is easily eliminated by the consideration that the value 22 kcals. includes the heat of evaporation which amounts to 9·5 kcals. (Goodeve and Richardson, *J.*, **1937**, 294).

Treatment of the mechanisms of reactions of oxygen–chlorine compounds on the lines developed above will assuredly lead to further simplifications and explanations.

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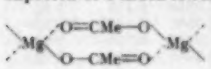
278. *Some Properties of the Calcium Salts of the Lower Fatty Acids. Part I. Viscosity.*

By W. B. BONNOR and C. G. SMITH.

The viscosities of aqueous solutions of calcium acetate, propionate, *iso*butyrate, and *iso*valerate were measured, and the results considered from the point of view of the Einstein and Guth–Simha equations, usually applied to systems of larger molecules. The high viscosity of these salts suggests a similarity with the behaviour of more complex molecules, and the agreement with the above equations substantiates this.

THE properties of the sols and gels formed when polar organic liquids are added to aqueous solutions of calcium acetate have been described by Thorne and Smith (*Kolloid-Z.*, **1929, 48, 113**) and by Smith (*ibid.*, **1931, 54, 181, 284**). The higher fatty acid salts of calcium, such as the propionate and the butyrate, form gels with organic liquids very much less readily, usually giving instead a fine-meshed mass of thin fibrous crystals. Hardly any other electrolytes are known to form gels in this way, and the question why calcium acetate should possess this remarkable property to such a considerable degree presents an interesting problem. Study of the gels themselves throws little light on the reason for their formation, and the present investigation was undertaken to discover whether this reason lay in the properties of the aqueous solutions.

Although the physical properties of aqueous solutions of alkali-metal salts of the fatty acid series have been extensively investigated, very little work has been undertaken upon the corresponding compounds of the alkaline earths. Only the lower members of this series are water-soluble to an appreciable extent, so that it was necessary to confine observations in aqueous solution to such salts as the formate, acetate, propionate, butyrate, and valerate. Except at very high dilution aqueous solutions of the alkali-metal salts of the higher fatty acids are colloidal electrolytes, micelle formation increasing with increase in the length of the carbon chain. The sodium salts of the lower members of the fatty acids appear not to form micelles, but the alkaline-earth salts contain twice as many carbon atoms as the corresponding sodium or potassium salts, and hence the onset of micelle or complex-anion formation may be expected at a much lower anionic weight. Rivett *et al.* (*J.*, **1926**, 1063; **1928**, 1950) suggested that in aqueous solutions of magnesium acetate complexes of the inset type are formed to an appreciable extent. Similar complexes in calcium acetate are a possibility which was kept in mind during this investigation. The known high viscosities of many solutions of electrolyte acetates suggest a high degree of solvation with, possibly, the formation of asymmetric complexes, and an attempt has been made to interpret viscosity data in this light.



EXPERIMENTAL.

Preparation and Purification of Materials.—The calcium acetate used was prepared by adding small amounts of AnalaR calcium carbonate to glacial acetic acid, well diluted with water, at room temperature. When an amount of calcium carbonate slightly in excess of the theoretical had been added, the mixture was set aside overnight, heated at 100° for 1—2 hours, filtered, and concentrated on a boiling water-bath until about 10% of the salt had been precipitated. The liquid was filtered whilst still hot (calcium acetate is less soluble in hot than in cold water). The precipitated calcium acetate was dissolved to saturation in cold water and the process of concentration repeated. The twice-precipitated salt was dried at the pump and heated to constant weight at 120° (Found : Ca, by precipitation as oxalate and titration with permanganate, 25·3—25·4%. Calc. for $C_4H_6O_4Ca$: Ca, 25·3%).

Calcium propionate and *iso*butyrate were prepared by twice crystallising commercial samples. Both

are more soluble in water at 100° than at room temperature. After being heated to constant weight at 120°, both gave satisfactory analyses for calcium.

A commercial sample of *iso*valeric acid was redistilled and calcium *iso*valerate prepared from it as described for calcium acetate. Calcium *iso*valerate is more soluble in cold than in hot water. The twice-precipitated material, dried at 120°, contained the theoretical amount of calcium within 0·2%.

The *n*-hexoic acid available was a dark brown liquid which did not freeze at −15°. This was redistilled, the colourless middle fraction, b. p. 201—202°/760 mm., being collected. Thirty times its weight of water was added, and AnalaR calcium carbonate was used for neutralisation. Calcium hexoate is only slightly soluble in water, and the difference between the solubilities in 100 g. of cold and hot water is only about 0·4 g. The material was therefore recrystallised only once. When dried at 120°, it contained 14·7% of calcium (Calc. for $C_{12}H_{22}O_4Ca$: Ca, 14·8%).

It was most important to remove all excess of fatty acid from the salts by heating to constant weight. Excess of acid is liable seriously to affect the properties of the solutions, particularly their viscosity. The pH of the pure aqueous solutions is between 8 and 9, and the pH was found to be a good check on freedom from excess of acid.

Determination of Viscosity.—Viscosity measurements were carried out in an Ostwald-type capillary viscometer which had the following dimensions: capacity of the upper bulb, about 10 ml.; radius of the capillary, 0·0201 cm.; length of capillary, about 18 cm.; time of flow for water at 18°, 185 seconds. Using the information given by De Jong ("First Report of Viscosity and Plasticity," Amsterdam, 1935, Chap. III), it was found that for this instrument the error due to eddying motion at the issuing jet should be less than 0·1%, and no kinetic energy correction was necessary.

The apparatus was cleaned with chromic acid solution before each day's determinations, and was kept filled with chromic acid when not in use. It was washed out with filtered water, and dried by passage of dust-free air. It was repeatedly re-calibrated by determining the time of flow for water. All determinations were carried out at a temperature kept within ±0·05° by a thermostat. Time of flow was determined to 0·1 second. In the calculation of the results, the densities determined by use of a 10-ml. pyknometer (repeatedly re-calibrated, constant ±0·002%) were employed. The results were not corrected for surface tension, but it appears that in an Ostwald viscometer of the usual shape this correction is small (Jones and Fornwalt, *J. Amer. Chem. Soc.*, 1938, **60**, 1683). The accuracy of the instrument was checked by measurement of the viscosity of sugar solutions at 15° and 30° (deviation from the International Critical Tables, −0·3% to −1·0%).

The solutions used were made by diluting known weights of saturated solutions with weighed quantities of water, and were checked against the concentrated solutions by evaporating 10-ml. portions to dryness, igniting and weighing the residue as calcium oxide.

Results.

The viscosities of solutions of calcium acetate, propionate, *iso*butyrate, *iso*valerate, and *n*-hexoate without and with added salts are recorded in Tables I—III.

In Table V are given the viscosities of a saturated solution of calcium propionate at different temperatures. The solution was saturated at 18°, and hence is slightly supersaturated at 25° and 30°, although crystallisation did not commence until 40°.

Table I.

Viscosities of aqueous solutions at 18°.

G./l.	Molarity (*c*).	$d_{18°}^{18°}$.	η/η_0.	$(\eta/\eta_0 - 1)/c$.	G./l.	Molarity (*c*).	$d_{18°}^{18°}$.	η/η_0.	$(\eta/\eta_0 - 1)/c$.
Calcium acetate:					Calcium propionate:				
14·95	0·0945	1·0084	1·085	0·90	17·8	0·0954	1·0088	1·099	1·04
30·4	0·192	1·0168	1·163	0·85	38·0	0·204	1·0180	1·210	1·03
60·1	0·380	1·0328	1·335	0·88	88·8	0·477	1·0412	1·591	1·24
112	0·708	1·0590	1·659	0·93	147·5	0·792	1·0668	2·173	1·48
149	0·942	1·0770	2·030	1·09	224	1·203	1·0987	3·195	1·825
196	1·240	1·0992	2·537	1·24	253	1·359	1·1102	3·740	2·02
237	1·498	1·1172	3·167	1·45	322 •	1·729	1·1380	6·216	3·02
252	1·596	1·1252	3·414	1·51					
306 •	1·935	1·1475	5·144	2·14					
Calcium *iso*butyrate:					Calcium *iso*valerate:				
15·9	0·0741	1·0068	1·095	1·28	14·1	0·0580	1·0052	1·084	1·45
32·1	0·150	1·0134	1·194	1·29	29·3	0·121	1·0101	1·175	1·45
45·2	0·211	1·0186	1·290	1·37	55·7	0·230	1·0189	1·359	1·56
89·3	0·417	1·0358	1·648	1·55	88·3	0·364	1·0294	1·641	1·76
133	0·620	1·0522	2·085	1·75	125	0·518	1·0410	2·085	2·10
180	0·748	1·0620	2·480	1·98	154	0·638	1·0498	2·551	2·44
194	0·905	1·0741	3·017	2·23	190 •	0·784	1·0804	3·260	2·88
Calcium *n*-hexoate:									
9·4	0·346	1·0026	1·055	1·59					
18·1	0·0668	1·0053	1·106	1·59					
21·9 •	0·0810	1·0063	1·130	1·60					

• Saturated solution.

TABLE II.

Viscosities of 1·828M-*calcium acetate, containing added salts, at* 18°.

Added sodium chloride,				Added calcium chloride,				Added sodium acetate,			
g./l. of water.	molarity.	d_{18}^{18}.	η/η_w.	g./l. of water.	molarity.	d_{18}^{18}.	η/η_w.	g./l. of water.	molarity.	d_{18}^{18}.	η/η_w.
0	0	1·1252	3·414	0	0	1·1252	3·414	0	0	1·1252	3·414
4·3	0·0524	1·1281	3·442	6·9	0·0622	1·1306	3·452	3·53	0·0604	1·1275	3·482
24·2	0·295	1·1344	3·636	25·9	0·233	1·1396	3·564	25·6	0·438	1·1382	3·584
63·0	0·768	1·1452	4·101	41·8	0·377	1·1475	3·629	47·3	0·809	1·1491	3·689
87·8	1·070	1·1499	4·395	63·2	0·569	1·1600	3·750	63·6	1·092	1·1568	3·772
				84·9	0·765	1·1695	3·859	85·0	1·454	1·1670	3·890

TABLE III.

Viscosities of 0·829M-*calcium* iso*butyrate, containing added salts, at* 18°.

Added sodium *iso*butyrate,				Added calcium chloride,			
g./l. of water.	molarity.	d_{18}^{18}.	η/η_w.	g./l. of water.	molarity.	d_{18}^{18}.	η/η_w.
0	0	1·0620	2·480	0	0	1·0620	2·480
1·83	0·0106	1·0630	2·491	5·8	0·0523	1·0656	2·497
13·0	0·118	1·0661	2·583	8·8	0·0793	1·0673	2·502
25·0	0·227	1·0680	2·694	26·1	0·235	1·0785	2·563
46·9	0·426	1·0708	2·909	35·6	0·321	1·0842	2·601
				45·5	0·410	1·0905	2·635
				55·2	0·497	1·0956	2·663

The decrease of viscosity caused by addition of acid is shown in Table IV.

TABLE IV.

Viscosity of 1·828M-*calcium acetate in acid and alkaline media at* 18°.

Medium.	pH.	d_{18}^{18}.	η/η_w.	Medium.	pH.	d_{18}^{18}.	η/η_w.
N/50-NaOH	11·0	1·1244	3·374	N-HCl	4·8	1·1307	2·873
Water	8·3	1·1252	3·414	2N-HCl	3·7	1·1391	2·472
N/50-HCl	7·0	1·1254	3·341				

TABLE V.

Viscosity of saturated calcium propionate solution.

Temp., ° c.	15	18	25	30
η/η_w	6·518	6·216	5·650	5·207

DISCUSSION.

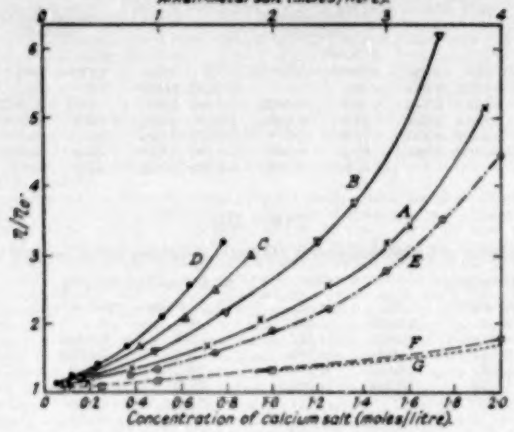
From Fig. 1 it will be seen that only at low concentrations is the viscosity linear with concentration, and that the relative viscosities of >1M-solutions rise steeply, reaching the order of 5 for saturated solutions.

Many electrolytes in very concentrated aqueous solution have viscosities several times greater than that of water. Thus the relative viscosities at 18° of 6M-calcium chloride and 10·03M-sodium hydroxide are 9·00 and 11·81 respectively. However, these solutions of acetates etc. are of the order of 2M. at the most, at which concentrations the other electrolytes mentioned have relative viscosities of 1·7 and 1·4 respectively.

The viscosity curve of sodium acetate is also plotted in Fig. 1 for comparison. The data for low concentrations was taken from the International Critical Tables, and a few determinations of the viscosity at higher concentrations were made by one of us (W. B. B.). The scale on abscissa has been doubled so that the concentration of acetate ions is comparable with that of the calcium salt. The viscosity of the sodium acetate is below that of the calcium at all concentrations, and the two curves are approximately parallel until the concentration of acetate ions reaches 3 g.-ions/l. Above this point, the viscosity of the calcium salt rises more steeply that that of the sodium. This is more clearly brought out in Fig. 3.

FIG. 1.

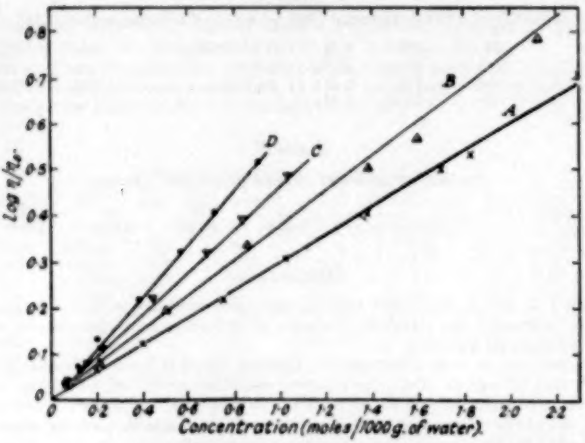
Viscosity of electrolyte solutions.



A = Calcium acetate. *B* = Calcium propionate. *C* = Calcium isobutyrate. *D* = Calcium isovalerate. *E* = Sodium acetate. *F* = Calcium chloride. *G* = Lithium chloride.

FIG. 2.

Application of Arrhenius equation.



A = Calcium acetate. *B* = Calcium propionate. *C* = Calcium isobutyrate. *D* = Calcium isovalerate.

A number of equations relating viscosity and solute concentration have been proposed, including:

(Einstein) $\eta/\eta_0 = 1 + h\phi$

(Guth and Simha) $\eta/\eta_0 = 1 + h\phi + K\phi^2$

(Arrhenius) $\log \eta/\eta_0 = Kc$

where ϕ is the volume fraction, and c the concentration.

Only Arrhenius's equation represents the data over the complete concentration range, as shown in Fig. 2, in which the logarithm of the relative viscosity is plotted against the molal concentration. Plots of viscosity against molarity depart appreciably from straight lines at higher concentrations.

The relation of the function $(\eta/\eta_0 - 1)/c$ to concentration is depicted in Fig. 3. In dilute solutions, the results agree with an equation of the Einstein form, but as the concentration rises, the curve corresponds to the Guth–Simha type, whilst at still higher values of the molar concentration, higher powers of c need to be added to the equation. In view of this, the Guth–Simha equation was solved for ϕ, and the function $(\eta/\eta_0 - 1)/\phi$ plotted against concentration (Fig. 4). It will be observed that the plots are almost linear over most of the range, suggesting that ratio of the concentration to the volume fraction is approximately constant, except for very dilute and very concentrated solutions. This corresponds to the constancy of the apparent degree of hydration inherent in the Guth–Simha equation; hydration is then responsible for the high viscosity (see Table VI.).

TABLE VI.

Moles/l.	η_r.	Guth–Simha, ϕ.	Volume fraction (v).	ϕ/v.	Apparent degree of hydration.
Calcium acetate :					
0·0945	1·085	0·029	0·0109	2·66	10·7
0·192	1·163	0·051	0·0220	2·32	8·48
0·380	1·335	0·0925	0·0435	2·12	7·3
0·708	1·659	0·145	0·0809	1·79	5·12
0·942	2·030	0·1952	0·108	1·81	5·4
1·240	2·537	0·252	0·142	1·78	5·18
1·498	3·167	0·312	0·1716	1·82	5·55
1·596	3·414	0·333	0·1822	1·83	5·58
1·935	5·144	0·461	0·2216	2·08	7·5
Calcium propionate :					
0·0954	1·099	0·0326	0·01416	2·30	10·17
0·204	1·21	0·0825	0·0302	2·07	8·9
0·477	1·591	0·1335	0·071	1·88	7·45
0·792	2·173	0·2125	0·1177	1·82	6·9
1·203	3·195	0·314	0·178	1·76	6·68
1·359	3·740	0·36	0·2018	1·79	7·07
1·729	6·216	0·525	0·256	2·05	9·27
Calcium *iso*butyrate :					
0·0741	1·095	0·0318	0·01258	2·52	14·42
0·150	1·194	0·0582	0·02543	2·28	12·42
0·211	1·290	0·0797	0·0358	2·22	11·64
0·417	1·648	0·1425	0·0708	2·02	9·6
0·620	2·085	0·2015	0·1052	1·92	8·88
0·748	2·480	0·246	0·127	1·935	9·15
0·905	3·017	0·298	0·1537	1·94	9·20
Calcium *iso*valerate :					
0·058	1·084	0·0284	0·0122	2·33	15·6
0·121	1·175	0·0536	0·0256	2·09	12·95
0·230	1·359	0·0934	0·0485	1·925	10·92
0·364	1·641	0·143	0·077	1·86	10·24
0·518	2·085	0·2015	0·109	1·845	10·18
0·636	2·581	0·254	0·134	1·895	10·88
0·784	2·88	0·326	0·165	1·975	11·9

According to Staudinger's theory, the limit of the function $(\eta/\eta_0 - 1)/c$, as c tends to zero, is proportional to the molecular weight of the solute, or in linear relation to it. Apart from the fact that the first members of an homologous series very often fail to obey the Staudinger law, no assistance can be expected from this approach in deciding whether or not association of the anions occurs, owing to the low dilutions used. The intrinsic viscosities of these substances have an approximately linear relation to the molecular weight, except, possibly, for the *iso*-compounds (Fig. 5).

Inserting the numerical coefficients usually employed in the Guth–Simha equation, thus :

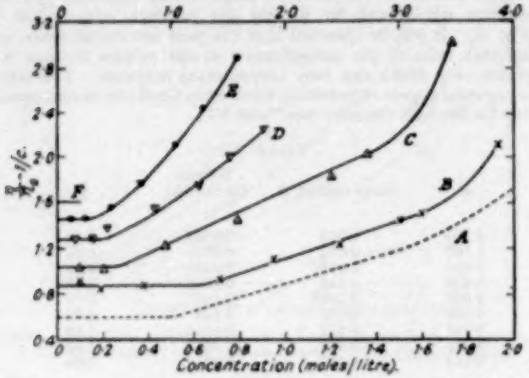
$$14{\cdot}1\phi^2 + 2{\cdot}5\phi + 1 - \eta/\eta_0 = 0$$

and solving for ϕ gives the results shown in Table VI. The volume fraction, given in column 4, was calculated from the molar volume in the solid state. This was chosen in preference to the

apparent molar volume calculated from the densities of the solution, because the latter includes the effect of the " tightening " of the water structure around the hydrated ions. Whilst it is realised that the volume of the ions in solution may not be the same as that in the solid, it is probable that at each concentration, these two volumes are in the same ratio to each other.

FIG. 3.

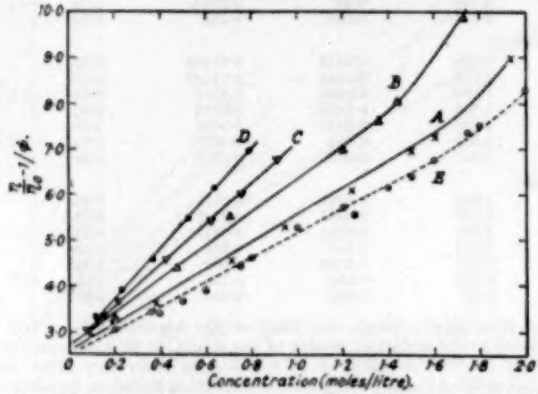
Application of Guth–Simha equation.



A = *Sodium acetate*. *B* = *Calcium acetate*. *C* = *Calcium propionate*. *D* = *Calcium isobutyrate*. *E* = *Calcium isovalerate*. *F* = *Calcium hexoate*.

FIG. 4.

Application of Guth–Simha equation.



A = *Calcium acetate*. *B* = *Calcium propionate*. *C* = *Calcium isobutyrate*. *D* = *Calcium isovalerate*. *E* = *Sodium acetate*.

Hence although the actual numerical results set out in the last three columns of Table VI are likely to be very approximate, the trend indicated reflects a change in the internal condition of the solution.

Over a wide range of concentration, the ratio ϕ/v is approximately constant. Since the volume fraction v calculated from the molar volume in the solid state is proportional to the

molarity, it can be a constant fraction of the Guth–Simha ϕ only whilst the apparent degree of hydration is constant. At low concentrations, this degree of hydration is high, but it falls rapidly as the concentration increases to a more or less constant value. It is not unreasonable

FIG. 5.
Staudinger's rule.

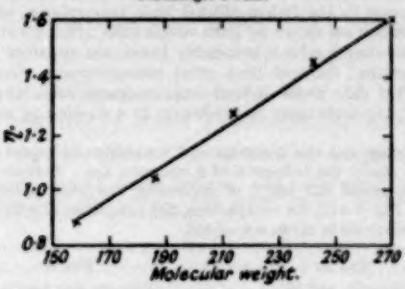
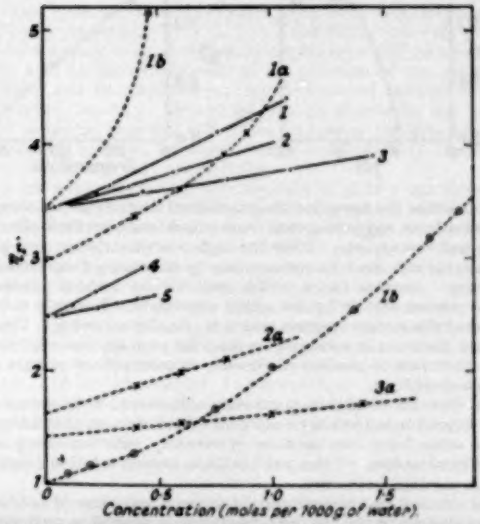


FIG. 6.
Viscosity of mixed solutions.



Calcium acetate solution containing (1) *sodium acetate*, (2) *calcium chloride, and* (3) *sodium chloride. Calcium* isobutyrate *solution containing* (4) *sodium* isobutyrate, *and* (5) *calcium chloride.* (1a) *Sodium acetate solution,* 3·65 M. *and higher.* (2a) *Calcium chloride solution,* 1·83 M. *and higher.* (3a) *Sodium chloride solution,* 3·65 M. *and higher.* (1b) *Calcium acetate solution.*

to assume that this corresponds to a real decrease in the hydration of the ions. However, the increase of viscosity at the higher concentrations is not likely to be due to any increase of real hydration, since the water is becoming scarcer. Since also the mere aggregation would not in itself increase viscosity, it may be assumed that this increase is caused by a development of symmetry of either shape or charge distribution, factors which would increase the internal

friction. It is also noticeable that the apparent degree of hydration is greater with the higher fatty acid salts. Since the anions depart more and more from hydrophilic character with increase of chain length, and the degree of hydration of the cation may be assumed uninfluenced by the anion, any increase of hydration is unlikely unless something in the nature of micelle formation, entrapping water, occurs. The increased viscosity again may be attributed to the increased asymmetry of the anion or anionic complex. This anionic complex may be of the same nature as the Debye–Hückel ionic atmospheres, for the same changes in apparent degree of hydration are shown by quite simple salts, although at higher concentrations. As the viscosity of these simple salts is invariably lower, the apparent degree of hydration is lower, often lower than that deduced from other measurements. Since fatty-acid ions are less likely to be hydrated than those derived from inorganic acids, the high viscosity of the calcium salts of these fatty acids must be attributed to a developing asymmetry of the anion complexes.

The purpose of determining the densities and viscosities of mixed solutions, recorded in Tables II—III, was to study the influence of a common ion. Sodium chloride was used for control experiments to assess the effect of increasing the ionic strength. The results are depicted graphically in Fig. 6 and, for comparison, the viscosities of solutions of the pure added salts over the same concentration range are added.

FIG. 7.
Viscosity and pH.

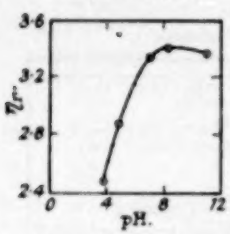
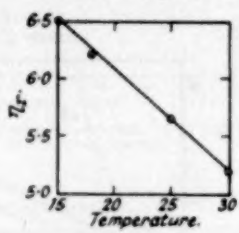


FIG. 8.
Viscosity and temperature.



It will be observed that the curve for the pure added electrolytes lies roughly parallel to the curves for the mixed solutes, suggesting that these added ions have little effect on the viscosities of calcium acetate and *iso*butyrate. Were the high viscosity due in any large degree to the presence of undissociated salt, then the common ion, by decreasing dissociation, should markedly increase the viscosity. Another factor which may not be without influence is the partial dehydration of the calcium acetate by the added electrolyte. Not only is this likely, but the eventual salting-out of the acetate suggests that it is actually occurring. This would reduce the viscosity, or at least maintain it constant, so that the increase observed is due solely to the added electrolyte. The rate of increase of viscosity of pure sodium acetate solution is greater than that of the mixed solution.

The decrease in viscosity of calcium propionate with rise of temperature (Fig. 8) points to the salt not being ionised in moderately concentrated solution, so that added ions would have no effect. On the other hand, the decrease of viscosity with increasing acidity (Fig. 7) is characteristic of an ionic system. "Neutral" calcium acetate solution (slightly alkaline owing to hydrolysis) shows maximum viscosity.

The addition of ethanol and *iso*propanol to aqueous solutions of calcium acetate, whilst causing certain irregularities in the viscosity, produces, in general, a preliminary diminution in the viscosity owing to dehydration, followed by an increase owing to the coalescence of the anionic complexes.

Conclusion.—The evidence on whether the high viscosity of these solutions is due to the anion or the un-ionised salt seems to be conflicting. Thus whilst neutral salts have little or no influence, pH of the medium is an important factor. The rapid increase at high concentration points to the formation of asymmetric anionic complexes, similar to, but simpler than, the micelles formed in soap solutions. These grow rapidly at higher concentrations and on dehydration (leading to salting out as gels or gelatinous precipitates), but are reduced by acidity or alkalinity (giving rise to acetic acid or alkali acetate).

Since high viscosity is characteristic of acetates etc. in concentrated solution, it may be concluded that it is the anions which are responsible. Compared with cations, these ions are not likely to be heavily hydrated, but anything in the nature of a micelle would entrap water, keeping the micelle small but giving a high viscosity. Removal of this water would permit agglomeration of the micelles, without necessarily increasing viscosity, any asymmetry effect being counteracted by dehydration of the micelles.

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279. *Studies of Trifluoroacetic Acid. Part II. Preparation and Properties of Some Trifluoroacetyl Esters.*

By E. J. BOURNE, (MRS.) C. E. M. TATLOW, and J. C. TATLOW.

The trifluoroacetyl esters of certain hydroxy- and polyhydroxy-compounds have been prepared under anhydrous conditions. Their properties are described; they are very susceptible to hydrolysis and to methanolysis.

SINCE the pioneering researches of Swarts (*Bull. Acad. roy. Belg., Classe Sci.*, **1922**, **8**, 343) on the preparation and properties of trifluoroacetic acid and of its ethyl ester, comparatively little attention has been paid to trifluoroacetyl esters. As far as we are aware, the only other trifluoroacetates which have been reported are methyl (Gryszkiewicz-Trochimowski *et al.*, *Rec. Trav. chim.*, **1947**, **66**, 419), vinyl (B.P. 589,197), 2 : 2 : 2-trifluoroethyl (Swarts, *Bull. Soc. chim. Belg.*, **1934**, **43**, 471), butyl (Henne, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, **1944**, 89), *iso*amyl (Swarts, *Bull. Soc. chim. Belg.*, **1927**, **36**, 191), and 2-methylbutadien-1-yl ("isoprene 1-yl") (U.S.P. 2,432,394). The only preparative methods so far employed which appear to be at all widely applicable entail (*a*) treatment of an alcohol with trifluoroacetic acid (or its sodium salt) in the presence of concentrated sulphuric acid (Swarts, *loc. cit.*, **1922**) and (*b*) condensation of trifluoroacetyl chloride with the appropriate sodium alkoxide (Henne, *loc. cit.*). Method (*a*) was too drastic for use in the carbohydrate series. Method (*b*) presented practical difficulties because of the gaseous nature of both the acid chloride and the acid bromide, for which Simons and Ramler (*J. Amer. Chem. Soc.*, **1943**, **65**, 389) quote b. p.s −27° and −5°, respectively.

Accordingly, in this work, trifluoroacetic anhydride (b. p. 39°) was chosen as the acylating agent and esterification was effected by warming the appropriate alcohol with the anhydride in the presence of dry sodium trifluoroacetate. Early attempts to isolate mannitol hexakistrifluoroacetate by pouring such a reaction mixture into aqueous sodium hydrogen carbonate solution indicated that the product was unstable under these conditions, so a standard method was devised by which the esters could be isolated under anhydrous conditions. The reaction mixture was distilled several times with dry carbon tetrachloride to remove excess of trifluoroacetic anhydride and trifluoroacetic acid, and the ester was extracted from the residual sodium trifluoroacetate with dry carbon tetrachloride or dry petroleum. By this means *p-nitrobenzyl trifluoroacetate*, *β-naphthyl trifluoroacetate*, D-*mannitol hexakistrifluoroacetate*, *dulcitol hexakistrifluoroacetate*, and 2 : 3-*bistrifluoroacetyl* 4 : 6-*benzylidene α-methylglucoside* were obtained crystalline, whilst 2 : 3 : 4 : 6-*tetrakistrifluoroacetyl α-methylglucoside* and 3 : 5 : 6-*tristrifluoroacetyl* 1 : 2-*isopropylidene* D-*glucofuranose* were isolated in the form of liquids.

Pyridine did not appear to be a suitable solvent in which to conduct esterifications using trifluoroacetic anhydride, since a mixture of the two rapidly darkened and left a brown solid when distilled.

The above trifluoroacetates were reasonably stable when pure and dry. They could be stored unchanged for several days in a vacuum over phosphoric oxide and, in certain cases, could be purified by distillation under diminished pressure. In the presence of water, however, they were readily hydrolysed, apparently by an autocatalytic reaction, to give the parent alcohol and trifluoroacetic acid. This property was very marked with the esters of polyhydroxy-compounds. Whereas we were unable to recover mannitol hexakistrifluoroacetate from any reaction mixture which was poured into water, most previous workers have employed this method for the isolation of trifluoroacetates which, however, have been derived hitherto from simple monohydric alcohols only. Thus it appears that two or more adjacent trifluoroacetoxy-groups are hydrolysed more readily than is an isolated substituent of this type.

We have found also that the above trifluoroacetates can be reconverted into their parent

alcohols by treatment with dry methyl alcohol under mild conditions. An indication of the ease with which this reaction proceeds was obtained polarimetrically in the case of mannitol hexakistrifluoroacetate. At 17°, the observed rotation of a dry methanolic solution of the ester fell to 70% of its original value in 1 hour and to zero overnight, by which time mannitol had crystallised out. The possibility of using methanolysis for the determination of trifluoroacetoxy-groups in the presence of other ester substituents is being examined.

It is noteworthy that, although the strength of trifluoroacetic acid approaches that of a mineral acid (Swarts, *loc. cit.*, 1922), a trifluoroacetyl residue, like acyl groups in general, is removed from an optically active ester without an accompanying Walden inversion or the formation of an anhydro-ring.

Experimental.

Precautions.—Unless otherwise stated, all operations involving trifluoroacetates were conducted with dry reagents under anhydrous conditions.

Preparation of Trifluoroacetic Anhydride.—The anhydride was prepared by the method of Swarts (*loc. cit.*, 1922), as modified by Bourne, Stacey, Tatlow, and Tedder (*J.*, 1949, 2976).

p-Nitrobenzyl Trifluoroacetate.—(a) *Preparation.* When *p*-nitrobenzyl alcohol (0·407 g.) was added to a mixture of trifluoroacetic anhydride (2·0 c.c.) and sodium trifluoroacetate (0·161 g.) a spontaneous reaction ensued. After being gently refluxed for 15 minutes, the homogeneous reaction mixture was distilled four times with carbon tetrachloride at 40—50° under slightly diminished pressure. The residue was extracted with three portions (15 c.c. each) of boiling light petroleum (b. p. 40—60°), filtered, and concentrated to a syrup, which crystallised. The product (0·502 g.), m. p. 46—48°, was decolorised with charcoal in boiling light petroleum and filtered. The filtrate deposited crystals of *p-nitrobenzyl trifluoroacetate* (0·232 g.), m. p. 47° (Found : CF_3·CO, 39·2. $C_9H_6O_4NF_3$ requires CF_3·CO, 38·95%).

(b) *Hydrolysis.* The neutral residues from the trifluoroacetyl estimation were extracted thrice with chloroform. The combined extracts were dried ($MgSO_4$), filtered, and concentrated, the solid residue being recrystallised from light petroleum (b. p. 100—120°) to give *p*-nitrobenzyl alcohol (yield, 73%), m. p. and mixed m. p. 93—95° (Found : C, 55·2; H, 4·4. Calc. for $C_7H_7O_3N$: C, 54·9; H, 4·6%).

(c) *Methanolysis.* A solution of *p*-nitrobenzyl trifluoroacetate (0·078 g.) in magnesium-dried methyl alcohol (10 c.c.) was kept at room temperature for 2 days. The solvent was removed under diminished pressure and the residue was crystallised from light petroleum (b. p. 100—120°). The product (0·030 g.) had m. p. 93—95°, alone and in admixture with authentic *p*-nitrobenzyl alcohol.

β-Naphthyl Trifluoroacetate.—(a) *Preparation.* β-Naphthol (0·800 g.), trifluoroacetic anhydride (3·50 c.c.), and sodium trifluoroacetate (0·301 g.) were gently refluxed for 15 minutes and then distilled thrice with carbon tetrachloride under slightly diminished pressure. The residue was extracted several times with boiling light petroleum (b. p. 40—60°) and filtered. The filtrate, concentrated to 5 c.c., deposited crystals of *β-naphthyl trifluoroacetate* (1·193 g.), m. p. 75—76°, unchanged by recrystallisation (Found : F, 23·4; CF_3·CO (end-point determined potentiometrically), 39·8. $C_{12}H_7O_2F_3$ requires F, 23·7; CF_3·CO, 40·4%).

(b) *Methanolysis.* A solution of β-naphthyl trifluoroacetate (0·176 g.) in magnesium-dried methyl alcohol (7 c.c.) was kept at 45° for 90 minutes before the solvent was removed under diminished pressure. The residue, recrystallised from light petroleum (b. p. 60—80°), afforded β-naphthol (0·078 g.), m. p. and mixed m. p. 122—123°.

D-*Mannitol Hexakistrifluoroacetate.*—(a) *Preparation.* D-Mannitol (0·307 g.), sodium trifluoroacetate (0·210 g.), and trifluoroacetic anhydride (6·50 c.c.) were gently refluxed for 2 hours, before being distilled four times with carbon tetrachloride under slightly diminished pressure. The residue was extracted with three portions (20 c.c. each) of boiling carbon tetrachloride. The combined extracts were filtered and, on cooling, the filtrate afforded the *ester* (1·054 g.), m. p. 54°. Recrystallised from carbon tetrachloride, it (0·804 g.) had m. p. 55—56°, $[\alpha]_D^{17}$ +24·1° (*c*, 1·77 in chloroform) (Found : F, 45·4; CF_3·CO, 75·8. $C_{18}H_8O_{12}F_{18}$ requires F, 45·1; CF_3·CO, 76·8%).

(b) *Hydrolysis.* D-Mannitol hexakistrifluoroacetate (0·100 g.) was dissolved at 21° in aqueous alcohol (10 c.c.; water, 20% by vol.) and kept at 21° for 20 hours, by which time $[\alpha]_D^{21}$ had fallen from +14·8° (4 minutes) to +0·0° and acidity had developed. The solution was evaporated at 70°/15 mm., and the residue crystallised from aqueous alcohol in needles (0·033 g.), m. p. 165—167°, alone and in admixture with authentic D-mannitol. Acetylation of the product afforded D-mannitol hexa-acetate in 62% yield, m. p. and mixed m. p. 122—123°, $[\alpha]_D^{21}$ +24·0° (*c*, 0·75 in chloroform).

(c) *Methanolysis.* The hexa-ester (0·299 g.) was dissolved at 17° in magnesium-dried methyl alcohol (10 c.c.) and kept at 17° for 20 hours, by which time needles had separated and $[\alpha]_D^{17}$ had fallen from +17·0° (2 minutes) to +0·0°. The crystalline product (0·041 g.) had m. p. 165°, alone and in admixture with authentic D-mannitol, and by acetylation gave D-mannitol hexa-acetate in 68% yield, m. p. and mixed m. p. 122—123°, $[\alpha]_D^{21}$ +24·5° (*c*, 0·86 in chloroform).

Dulcitol Hexakistrifluoroacetate.—(a) *Preparation.* Dulcitol (0·298 g.), sodium trifluoroacetate (0·206 g.), and trifluoroacetic anhydride (4·50 c.c.) were gently refluxed for 75 minutes. The homogeneous reaction mixture, treated as in the case of the mannitol ester, yielded *dulcitol hexakistrifluoroacetate* in white plates (0·990 g.), m. p. 89—91°, unchanged by recrystallisation (Found : F, 44·95; CF_3·CO, 77·0. $C_{18}H_8O_{12}F_{18}$ requires F, 45·1; CF_3·CO, 76·8%).

(b) *Methanolysis.* This ester (0·286 g.) was heated for 45 minutes with boiling magnesium-dried methyl alcohol (5 c.c.). Crystals of dulcitol (0·060 g.) were deposited on cooling, m. p. and mixed m. p. 186—188° (Found : C, 39·8; H, 7·5. Calc. for $C_6H_{14}O_6$: C, 39·55; H, 7·75%).

2 : 3 : 4 : 6-*Tetrakistrifluoroacetyl* α-*Methyl*-D-*glucopyranoside.*—(a) *Preparation.* α-Methylglucoside (0·537 g.), sodium trifluoroacetate (0·202 g.), and trifluoroacetic anhydride (4·50 c.c.) were gently refluxed for 15 minutes and then treated as in the case of *p*-nitrobenzyl trifluoroacetate. The residual syrup,

which did not crystallise, was distilled at 158—160° (bath temp.)/12 mm. to give a clear colourless oil (0·945 g.), n_D^{25} 1·3641, $[\alpha]_D^{25}$ +88° (*c*, 0·88 in carbon tetrachloride) (Found : F, 39·1; $CF_3{\cdot}CO$, 67·25. $C_{11}H_{19}O_{10}F_{11}$ requires F, 39·4; $CF_3{\cdot}CO$, 67·1%).

(b) *Methanolysis*. 2 : 3 : 4 : 6-*Tetrakistrifluoroacetyl* α-*methyl*-D-*glucopyranoside* (0·037 g.) was dissolved at 15° in magnesium-dried methyl alcohol (5 c.c.) and after 16 hours the solvent was removed at 40°/12 mm. The crystalline residue, recrystallised from methyl alcohol–ether, afforded α-methylglucoside (0·009 g.), m. p. and mixed m. p. 164—167°.

2 : 3-*Bistrifluoroacetyl* 4 : 6-*Benzylidene* α-*Methyl*-D-*glucopyranoside*.—(a) *Preparation*. When 4 : 6-benzylidene α-methylglucoside (3·039 g.), sodium trifluoroacetate (0·223 g.), and trifluoroacetic anhydride (6·60 c.c.) were mixed a vigorous reaction ensued. After several minutes, the reaction mixture was distilled under slightly diminished pressure with four portions (20 c.c. each) of carbon tetrachloride, and the residue was extracted with three portions (20 c.c. each) of boiling carbon tetrachloride. The combined extracts were filtered and evaporated to a syrup, which crystallised. Recrystallised twice from light petroleum (b. p. 40—60°), the *bistrifluoroacetyl* compound (1·522 g.) had m. p. 88—89°, $[\alpha]_D^{25}$ +77·6° (*c*, 0·80 in carbon tetrachloride). Although the ester was appreciably soluble in cold light petroleum, it appeared to be far more soluble in all the other common organic solvents and hence high losses during recrystallisation were inevitable (Found : F, 24·1; $CF_3{\cdot}CO$, 41·15. $C_{15}H_{14}O_8F_6$ requires F, 24·0; CF_3CO, 40·9%).

(b) *Hydrolysis*. The titration liquors from the trifluoroacetyl determination were made just alkaline to phenolphthalein, and the acetone removed under diminished pressure. The aqueous residue was extracted with chloroform. The extract was dried ($MgSO_4$), filtered, and evaporated, leaving a solid, which was recrystallised from water in the presence of a trace of ammonia. The product, isolated in 62% yield, had m. p. 163°, not depressed in admixture with 4 : 6-benzylidene α-methylglucoside, $[\alpha]_D^{25}$ +115° (*c*, 0·50 in chloroform) (Found : C, 59·6; H, 6·4. Calc. for $C_{14}H_{18}O_6$: C, 59·55; H, 6·4%).

(c) *Methanolysis*. A solution of the bistrifluoroacetate (0·058 g.) in magnesium-dried methyl alcohol (5 c.c.) was kept at room temperature for 18 hours. Evaporation of the solvent under diminished pressure afforded 4 : 6-benzylidene α-methylglucoside (0·034 g.).

3 : 5 : 6-*Tristrifluoroacetyl* 1 : 2-*iso*-*Propylidene* D-*Glucofuranose*.—(a) *Preparation*. *iso*Propylidene glucose (0·802 g.), sodium trifluoroacetate (0·207 g.), and trifluoroacetic anhydride (3·85 c.c.) were gently refluxed for 15 minutes and treated as in the case of the above benzylidene derivative. The resulting product, which failed to crystallise, was distilled at 163—165° (bath temp.)/12 mm. to give a colourless viscous syrup (1·490 g.), $[\alpha]_D^{25}$ +15·7° (*c*, 1·20 in carbon tetrachloride) (Found : F, 33·1; $CF_3{\cdot}CO$, 58·3. $C_{15}H_{19}O_9F_9$ requires F, 33·6; $CF_3{\cdot}CO$, 57·25%).

(b) *Methanolysis*. The *ester* (0·134 g.) was gently refluxed with magnesium-dried methyl alcohol (20 c.c.) for 1 hour. Removal of the solvent under diminished pressure left a solid, which was recrystallised from ethyl acetate, giving mono*iso*propylidene glucose (0·041 g.), m. p. and mixed m. p. 161—163°.

Analytical Methods.—(a) *Trifluoroacetyl determination*. The trifluoroacetate (equivalent to *ca.* 8 c.c. of 0·05N-sodium hydroxide) was dissolved in acetone (5 c.c.) and 0·05N-sodium hydroxide (10·0 c.c.) was added. After 6—15 hours the excess of alkali was titrated with 0·015N-hydrochloric acid, phenolphthalein being used as the indicator.

(b) *Fluorine determination*. The method employed was that reported by Musgrave, Smith, and Tatlow (*J.*, 1949, 3021).

The authors express their thanks to Professor M. Stacey for his interest and encouragement in this work, and acknowledge the help of Imperial Chemical Industries Ltd. (General Chemicals Division) in providing part of the trifluoroacetic acid used in the investigation. They also thank Mr. R. Belcher and Mr. S. J. Clark for carrying out the fluorine analyses. One of them (C. E. M. T.) is indebted to the Colonial Products Research Council for the award of a scholarship.

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280. *A Synthesis of* 2-(2 : 3-*Dimethoxyphenyl*)cyclo*hexanone*.

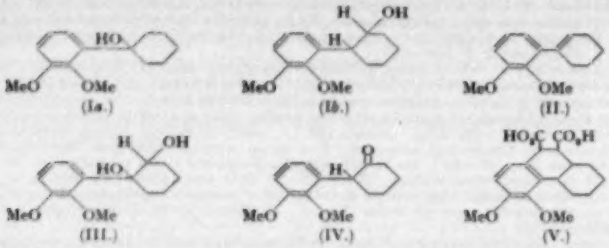
By ERNST D. BERGMANN, RAPHAEL PAPPO, and DAVID GINSBURG.

2-(2 : 3-Dimethoxyphenyl)*cyclo*hexanone is prepared, starting from 2 : 3-dimethoxyphenyllithium and *cyclo*hexanone or epoxy*cyclo*hexane. Intermediates are elucidated.

FOR a synthetic project, relatively large quantities of 2-(2 : 3-dimethoxyphenyl)*cyclo*hexanone (IV) were required. The methods chosen may be of interest in connection with the results recently communicated by Mueller and May (*J. Amer. Chem. Soc.*, 1949, **71**, 3313). 2 : 3-Dimethoxyphenyl-lithium, which is obtained from veratrole and butyl-lithium (Gilman, Swiss, and Cheney, *ibid.*, 1940, **62**, 1965), gave with 2-chloro*cyclo*hexanone rather intractable mixtures containing only traces of ketonic material, probably because of the multiplicity of possible simultaneous reactions (Newman and Booth, *J. Org. Chem.*, 1947, **12**, 737; Orchin, *J. Amer. Chem. Soc.*, 1948, **70**, 495). The following two alternative methods gave overall yields of 21%.

Condensation of 2 : 3-dimethoxyphenyl-lithium with *cyclo*hexanone or with *cyclo*hexene oxide (cf. Cook, *J.*, 1936, 71) yielded (I*a*) and 2-(2 : 3-*dimethoxyphenyl*)cyclo*hexan*-1-*ol* (I*b*), respectively.

(I*b*) was oxidised directly to 2-(2 : 3-*dimethoxyphenyl*)cyclo*hexanone* (IV) with chromic acid in glacial acetic acid, but for the conversion of (I*a*) into (IV) the following more devious route was



used: (I*a*) split off water easily upon treatment with oxalic acid in boiling toluene. The hydroxylation of 1-(2 : 3-*dimethoxyphenyl*)cyclo*hexene* (II) so obtained led to the *glycol* (III), both when performic acid and when osmium tetroxide was used. The same glycol also resulted from the direct interaction of the carbinol (I*a*) with performic acid. Oxalic acid caused transformation of the glycol into the desired ketone (IV). The direct oxidative transformation of (I*b*) into (IV) proves the constitution of the former.

The ketone (IV) proved identical with the substance synthesized by Horning, Horning, and Platt (*J. Amer. Chem. Soc.*, 1947, **69**, 2929) from 2 : 3-dimethoxybenzaldehyde by a much longer route and in an overall yield of 6·4%. The olefin (II) gave a very unstable dibromide; it is, however, easily characterised by the reaction with maleic anhydride which yields a crystalline *dicarboxylic acid* (V). This reaction conforms with the results of Szmuszkovicz and Modest (*J. Amer. Chem. Soc.*, 1948, **70**, 2542) but it is smoother than that of 1-phenyl*cyclo*hexene studied by these authors.

It is perhaps surprising that the osmium tetroxide and the performic acid method of hydroxylation generally believed to give *cis*- and *trans*-glycols, respectively, should lead to the same glycol (III). This is by no means characteristic for the *cyclo*hexene system, as English and Gregory (*ibid.*, 1947, **69**, 2120) have obtained without difficulty the *trans*-diol from *cyclo*hexene itself.

Neither the treatment with aluminium *tert.*-butoxide and acetone or *cyclo*hexanone, nor the interaction with *N*-bromosuccinimide (following a suggestion by Prof. L. F. Fieser), caused the expected dehydrogenation of the secondary hydroxyl group in (III), but the structure of the glycol appears firmly established by the rearrangement to (IV). Indeed, in the case of 1-phenyl*cyclo*hexane-1 : 2-diol, too, only one form is stable, which rearranges to 2-phenyl*cyclo*hexanone; it has been shown to be the *cis*-compound (Nametkin and Iwanoff, *Ber.*, 1923, **56**, 1806; Nametkin, *Chem. Zentr.*, 1925, I, 222; 1926, I, 2686; Böeseken, *Ber.*, 1923, **56**, 2409; Verkade, *Annalen*, 1928, **467**, 232). It is reasonable to assume that the glycol (III) also has the *cis*-configuration.

Experimental.

(All b. p.s and m. p.s are uncorrected.)

1-(2 : 3-*Dimethoxyphenyl*)cyclo*hexanol* (I*a*).—A solution of 2 : 3-dimethoxyphenyl-lithium was prepared from ethereal butyl-lithium [from 164 g. (1·2 mols.) of butyl bromide and 18·5 g. of lithium wire] and veratrole (200 g., 1·5 mols.) in ether (1200 c.c.). The reaction was interrupted after 24 hours at room temperature (stirring); it was desirable to protect the reacting mixture from autoxidation by a slow current of nitrogen.

To this solution, *cyclo*hexanone (110 g., 1·1 mols.) in anhydrous ether (150 c.c.) was added at −10° to 0°, with stirring. After 12 hours, the reaction product was treated with ice-water, and hydrochloric acid added until reaction was neutral. The ethereal solution was then washed with water, 10% sodium hydroxide solution, and water, and then concentrated and the residue was subjected to vacuum-distillation (b. p. 130—145°/0·03 mm.) (120 g.). The very viscous oily *alcohol* crystallised spontaneously. After recrystallisation from light petroleum the substance melted at 51—51·5°. The yield was 90 g. (Found: C, 71·0, 71·4; H, 8·9, 8·7. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·5%).

From the fore-run, veratrole (113 g.) could be recovered by renewed fractionation. Calculated on veratrole reacting, the yield of (I*a*) is 60%.

2-(2 : 3-*Dimethoxyphenyl*)cyclo*hexanol* (I*b*).—The solution of 2 : 3-dimethoxyphenyl-lithium was prepared as above [from 90 g. (0·66 mol.) of butyl bromide, 9 g. of lithium wire, and 100 g. (0·75 mol.) of veratrole in 300 c.c. of ether]. At 5°, *cyclo*hexene oxide (50 g., 0·50 mol.) was added. When the spontaneous reaction had subsided, the mixture was refluxed for 2 hours and the product hydrolysed by

addition of cold water. From the ethereal solution 2-(2 : 3-*dimethoxyphenyl*)cyclo*hexanol* (Ib) was isolated by fractionation (b. p. 140—150°/0·02 mm.) as a very viscous liquid which crystallised on trituration with methylcyclohexane. The alcohol (35 g.) crystallised from the same solvent in well-shaped crystals, m. p. 67—68°. Based on the veratrole not recovered (46 g.), the yield amounted to 70% (Found : C, 70·8; H, 8·5. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·5%).

1-(2 : 3-*Dimethoxyphenyl*)cyclo*hexene* (II).—Dehydration of (Ia) (15 g.) was effected by heating it with anhydrous oxalic acid (2 g.) in boiling toluene (50 c.c.), until no more water collected in the azeotropic separator (~30 minutes). The yield of colourless cyclo*hexene*, m. p. 14·2°, b. p. 145—150°/0·01 mm., was quantitative (Found : C, 77·4; H, 8·6. $C_{14}H_{18}O_2$ requires C, 77·1; H, 8·3%).

The dehydration of (Ia) with formic acid according to Sherwood, Short, and Stansfield (*J.*, 1932, 1832) was unsatisfactorily slow and gave rise to highly coloured tars.

The *dibromide*, prepared in light petroleum at −5°, crystallized spontaneously. It decomposes readily even at only slightly elevated temperature. It melts at 130° (decomp.) if brought into a bath preheated at 128° (Found : Br, 42·3, 42·6. $C_{14}H_{18}O_2Br_2$ requires Br, 42·4%).

Reaction of (II) *with Maleic Anhydride.*—A mixture of (II) (3 g.) and maleic anhydride (10 g.) was refluxed for 3 hours in the presence of a few crystals of *N*-phenyl-α-naphthylamine (the same result was achieved by heating the mixture at 120° for 48 hours). The reaction product was dissolved in 10% aqueous sodium hydroxide and precipitated with hydrochloric acid. Recrystallised from glacial acetic acid 3 : 4-*dimethoxy*-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-*octahydrophenanthrene*-9 : 10-*dicarboxylic acid* (X) had m. p. 173—175° (decomp.) It contained no olefinic double bonds (titration with perbenzoic acid) (Found : C, 65·1, 65·3; H, 6·4, 6·4%; equiv., 168·5. $C_{18}H_{22}O_6$ requires C, 64·6; H, 6·3%; equiv., 167).

1-(2 : 3-*Dimethoxyphenyl*)cyclo*hexane*-1 : 2-*diol* (III).—(*a*) To a solution of (II) (10·8 g.) in 90% formic acid (33 c.c.), 30% hydrogen peroxide (6 g.) was added with stirring, the temperature being kept below 40°. The mixture became homogeneous after 15 minutes. After 2 hours, the formic acid was removed *in vacuo* and the residue refluxed for 1 hour with potassium hydroxide (9 g.) in methanol (50 c.c.). The methanol was distilled off; the *product*, taken up with water, extracted with ether, and recrystallised from methylcyclohexane, had m. p. 104—105° (7·3 g.) [Found : C, 66·5; H, 8·6; active H, 1·8 (Zerewitinoff). $C_{14}H_{20}O_4$ requires C, 66·6; H, 8·0%; active H, 2·0]. From the mother-liquor, a second crop (0·4 g.) of the same substance, and 1·5 g. of unchanged starting material could be recovered by fractionation *in vacuo*. The total yield was 70%. In subsequent runs the yield varied from 70 to 80%.

(*b*) From (II) (0·8 g.) and osmium tetroxide (1·0 g.), 0·8 g. of (III), m. p. 104—105°, was obtained by Wieland's procedure (*Ber.*, 1912, **75**, 1708). Mixed m. p. of samples formed by procedure (*a*) and (*b*) showed no depression.

Reaction of (III) *with* N-*Bromosuccinimide.*—A solution of (III) (2 g.) and the reagent (2 g.) in a mixture of dioxan (20 c.c.) and water (2 c.c.) gave, after 24 hours at room temperature, a quantitative yield of a *monobromo*-compound, m. p. 118—120°, instead of the expected oxidation product (Found : Br, 24·2, 24·3. $C_{14}H_{19}O_4Br$ requires Br, 24·2%). The bromine atom probably entered the benzene nucleus.

2-(2 : 3-*Dimethoxyphenyl*)cyclo*hexanone* (IV).—(*a*) A mixture of the diol (III) (25·2 g.) and anhydrous oxalic acid (10 g.) was heated at 110—120° for 30 minutes. The product was isolated by treatment with aqueous sodium hydroxide and ether; after removal of the solvent, it crystallised spontaneously and was recrystallised from light petroleum (yield, 11 g., m. p. 70—71°). The 2 : 4-dinitrophenylhydrazone melted at 125—127°, and the oxime at 139—140°. According to Horning, Horning, and Platt (*loc. cit.*), the three m. p.s are 67—68·5°, 123—124°, and 137—138° (all corrected), respectively.

(*b*) When (Ib) was oxidised with chromic acid in glacial acetic acid, according to Cook (*loc. cit.*), a 30% yield of (IV) was obtained. The substance and its 2 : 4-dinitrophenylhydrazone proved identical with the corresponding products prepared according to procedure (*a*).

This paper represents part of a thesis submitted by Raphael Pappo to the Hebrew University, Jerusalem, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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281. *The Selenoaldehydes. Part I.* "*Selenoformaldehyde*" (*Trimethylene Triselenide*) *and its Chlorination Products.*

By H. J. Bridger and R. W. Pittman.

Three products of the interaction of hydrogen selenide and formaldehyde are described. Two of them are solids and have been previously reported; the third is a liquid which appears to have been hitherto unmentioned. The name selenoformaldehyde, previously applied to the two solid products, is not compatible with their properties and trimethylene triselenide is proposed as an alternative.

Chlorination of the higher-melting form of trimethylene triselenide, resulting in the isolation of bischloromethyl selenide, bischloromethyl diselenide, and chloromethylselenenyl chloride, is also described.

According to the concentration of hydrochloric acid present, one or another of three products is obtained on passing hydrogen selenide into aqueous solutions of formaldehyde. At high acid concentrations, a light-yellow powder, m. p. *ca.* 200°, is produced, at medium acid concentrations, a pasty solid, m. p. $< 100°$, and at low acid concentrations or in neutral solution a heavy, colourless, unpleasant-smelling oil.

The first two products have been prepared by earlier workers (Vanino and Schinner, *J. pr. Chem.*, 1915, [ii], **91**, 116 : Bradt and Valkenburgh, *Proc. Indiana Acad. Sci.*, 1929, **39**, 165; Pearson, Purcell, and Saigh, *J.*, 1938, 409), but the oil has not been previously recorded, though sulphur analogues have been described (Baumann, *Ber.*, 1890, **23**, 60; Pinner, *Ber.*, 1871, **4**, 257). The inter-relations of these materials are still being investigated and will form the subject of a later publication.

The work recorded here is only concerned with the higher-melting solid. This compound is relatively unreactive, is unaffected by boiling concentrated hydrochloric acid and aqueous caustic alkalis, is only slowly, but completely, decomposed by hot concentrated sulphuric acid, and shows no signs of reaction with the standard reagents used for the detection of carbonyl groups. It is insoluble in water and only sparingly soluble in most organic solvents. It is, however, sufficiently soluble in xylene and in chlorobenzene to allow it to be purified by recrystallisation from these solvents. The purified product consists of practically odourless, white, needle-like crystals, m. p. 210°. Analytical figures correspond with the formula $(CH_2Se)_3$. Vanino and Schinner obtained similar figures and unfortunately named this compound selenoformaldehyde and this terminology still persists. When, however, the properties of formaldehyde and trithioformaldehyde are reviewed in conjunction with the relative bond strengths of singly- and double-bonded oxygen, sulphur, and selenium, it seems highly unlikely that monomeric selenoaldehydes should exist at all; this substance is therefore probably a polymer, and molecular-weight determinations in boiling xylene indicate that it is, in fact, a trimer. It is probably cyclic, similar in structure to trioxymethylene and trithioformaldehyde, and thus to be considered rather as a cyclic selenide than as an analogue of formaldehyde. It exhibits no properties similar to those of the aldehydes and its chemical behaviour resembles that of the simple organic selenides, for example, in the formation of insoluble addition compounds with many metallic salts (Pearson, Purcell, and Saigh, *loc. cit.*). The name trimethylene trieselenide is therefore more in accord with its probable structure and properties.

Attempts were made to carry out a controlled oxidation of trimethylene triselenide, in a manner similar to that used by Bell and Bennett (*J.*, 1929, 15) in the preparation of sulphoxides from trithioformaldehyde. Hydrogen peroxide and nitric acid were used and the conditions were widely varied, but without success, only hydrated selenious and selenic acids being isolated.

Chlorination, first accomplished by passing gaseous chlorine into a well-stirred suspension of trimethylene triselenide in carbon tetrachloride, gave, in addition to elementary selenium and unidentifiable gummy substances, bischloromethyl selenide, bischloromethyl diselenide, and chloromethylselenenyl chloride.

It was found later that chlorination with selenium monochloride gave the same products. If the proportion of chlorinating agent used was kept at a minimum, bischloromethyl selenide and diselenide only, were isolated, but, if excess was used, the product consisted almost entirely of the selenenyl chloride.

Bischloromethyl selenide is a pale yellow mobile liquid with a smell surprisingly reminiscent of the simpler chlorinated hydrocarbons. It is fairly stable to heat and can be distilled unchanged at atmospheric pressure (b. p. 42°/2 mm., 180°/760 mm.). It is insoluble in water but miscible with most organic solvents. Boiling water attacks it but little, and it can be distilled from strong aqueous sodium hydroxide. However, it is hydrolysed fairly readily to formaldehyde and trimethylene triselenide by boiling aqueous solutions of sodium hydrogen carbonate or borate, the latter being the more effective :

$$2H_2O + (Cl{\cdot}CH_2)_2Se \longrightarrow 2HCl + CH_2O + OH{\cdot}CH_2{\cdot}SeH$$
$$3(HO{\cdot}CH_2{\cdot}SeH) \longrightarrow (H_2CSe)_3 + 3H_2O \ .$$

This may be compared with similar reactions of the analogous sulphur compounds (Bloch and Hohn, *Ber.*, 1922, **55**, 53).

Treatment with aqueous potassium iodide liberates no iodine, indicating that chlorine is not directly attached to selenium, and this is confirmed by treatment with iodine monochloride, which liberates two equivalents of iodine per atom of selenium :

$$SeR_2 + 2ICl \longrightarrow R_2SeCl_2 + I_2$$

Bischloromethyl diselenide is a heavy golden-yellow oil, which does not wet glass. In odour it slightly resembles the organic selenides. It has b. p. 97°/1·5 mm., but it is impossible to measure the boiling point at atmospheric pressure, owing to extensive decomposition, at elevated temperatures, to selenium and bischloromethyl selenide in fair yield. The diselenide

is insoluble in water, and sparingly soluble in methyl alcohol, but readily soluble in the less polar organic solvents. Like the selenide it is hydrolysed with some difficulty. The hydrolytic products are sticky intractable solids.

No iodine is produced on treatment with aqueous potassium iodide, and three equivalents of iodine per atom of selenium are liberated on treatment with iodine monochloride, thus confirming the presence of the diselenide link :

$$Se_2R_2 + 6ICl \longrightarrow 2R{\cdot}SeCl_3 + 3I_2$$

This linkage is somewhat labile : in addition to the thermal decomposition, treatment with potassium cyanide gives an evil-smelling mixture from which potassium selenocyanate and bischloromethyl selenide can be isolated :

$$(Cl{\cdot}CH_2{\cdot}Se)_2 \longrightarrow Se(CH_2Cl)_2 + Se$$
$$Se_2R_2 + KCN \longrightarrow SeR_2 + KSeCN$$

The latter reaction resembles the attack on the disulphide linkage by potassium cyanide, described by Farnworth and Speakman (*Nature*, 1949, **163**, 798). The diselenide link is also readily cleaved by halogens : *e.g.*, treatment with chlorine gives an almost theoretical yield of the selenenyl chloride.

Chloromethylselenenyl chloride is a dark red heavy oil, b. p. 52°/1·5 mm., which does not wet glass and has a smell resembling that of burnt gunpowder. It is soluble in most organic solvents but insoluble in water, by which it is, however, rapidly hydrolysed. It is much less stable and more reactive than the two compounds described above. When it is kept for several weeks, black crystals of selenium are deposited and hydrogen chloride is evolved. On heating, disproportionation occurs and this renders the purification of the material somewhat difficult, as bischloromethyl selenide and diselenide continue to distil even on repeated fractionation at pressures as low as 0·5 mm. This behaviour may be represented as resulting from the simultaneous occurrence of the two reactions :

$$3Cl{\cdot}CH_2{\cdot}SeCl \longrightarrow Cl{\cdot}CH_2{\cdot}SeCl_3 + (Cl{\cdot}CH_2{\cdot}Se)_2$$
$$Cl{\cdot}CH_2{\cdot}SeCl_3 + Cl{\cdot}CH_2{\cdot}SeCl \longrightarrow (Cl{\cdot}CH_2)_2Se + SeCl_4$$

Foster (*Rec. Trav. chim.*, 1934, **53**, 405) found a similar disproportionation on heating arylselenium halides.

The hydrolysis products obtained on treating chloromethylselenenyl chloride with water or dilute alkali include a sticky, so far unidentifiable yellowish-white solid, red selenium, and bischloromethyl diselenide. Behagel and Siebert (*Ber.*, 1933, **66** *B*, 708) found a similar production of diselenides on hydrolysis of the arylselenenyl chlorides and suggested the following mechanism :

$$R{\cdot}SeCl + H_2O \longrightarrow R{\cdot}Se{\cdot}OH + HCl$$
$$2R{\cdot}Se{\cdot}OH \longrightarrow R{\cdot}SeH + R{\cdot}SeO_2H$$
$$R{\cdot}Se{\cdot}OH + SeRH \longrightarrow Se_2R_2 + H_2O$$

The direct attachment of a chlorine atom to selenium in this compound is indicated by the liberation of one equivalent of iodine per atom of selenium on treatment with aqueous potassium iodide :

$$2Cl{\cdot}CH_2{\cdot}SeCl + 2KI \longrightarrow (Cl{\cdot}CH_2{\cdot}Se)_2 + 2KCl + I_2$$

and this is supported by the production of two equivalents of iodine by interaction with iodine monochloride :

$$Cl{\cdot}CH_2{\cdot}SeCl + 2ICl \longrightarrow Cl{\cdot}CH_2{\cdot}SeCl_3 + I_2$$

From the fact that on treating trithioformaldehyde with sulphur dichloride they obtained an almost quantitative yield of products according to the equation

$$(CH_2S)_3 + 2SCl_2 \longrightarrow (Cl{\cdot}CH_2)_2S + CS_2 + 2HCl + 2S$$

Mann and Pope (*J.*, 1923, 1172) appear to adduce some support for a cyclic structure for trithioformaldehyde. A similar suggestion that bischloromethyl selenide obtained by the chlorination of trimethylene triselenide is formed from the fragments of the triselena*cyclo*hexane ring is attractive. However, if this is accepted, difficulties immediately arise with respect to the explanation of the formation of bischloromethyl diselenide. Also, it must be remembered that the chlorination of monomeric carbon diselenide (Ives, Pittman, and Wardlaw, *J.*, 1947, 1080) gives rise to a series of compounds exactly analogous with those described in this paper. It is therefore necessary to conclude that chlorination of trimethylene triselenide offers little support for a ring structure for this compound.

It seems highly likely that the initial product in the chlorination is chloromethylselenenyl chloride, which, in the absence of excess of chlorinating agent readily loses chlorine with the formation of the diselenide, and that the bischloromethyl selenide which may be subsequently obtained is produced by the disproportionation of this compound in the distillation necessary for purification.

Experimental.

Interaction of Formaldehyde and Hydrogen Selenide.—(a) *In strongly acid solution* (Vanino and Schinner, *loc. cit.*). Hydrogen selenide was passed over the surface of a well-stirred mixture of 36% formaldehyde (30 g.) and concentrated hydrochloric acid (90 ml.) in an air-free apparatus, until no more absorption occurred. The white solid which formed was filtered off and washed free from hydrogen selenide with a large quantity of water, followed by alcohol and then by ether. It was dried in a vacuum-desiccator for several weeks. Yield, 30 g. Recrystallisation twice from xylene gave trimethylene triselenide as white needles, m. p. 210°, unchanged on further recrystallisation (Found: Se, 84·4%; *M* (ebullioscopic in xylene), 262. Calc. for $(CH_2Se)_3$: Se, 85·0%; *M*, 279). Unless it was adequately dried, the compound appeared not to be soluble in either xylene or chlorobenzene.

(b) *At medium acid concentration.* The previous experiment was repeated using a mixture of 36% formaldehyde (30 g.), concentrated hydrochloric acid (30 ml.), and water (60 ml.). A white evil-smelling pasty solid was obtained. This was repeatedly washed with alcohol and then with acetone and dried in a vacuum desiccator. This substance could not be recrystallised from any of the common organic solvents. It had m. p. 70—74°, but, when the substance was kept, the m. p. slowly rose to 165° (Found: Se, 79·3%). On vacuum-sublimation (<0·0001 mm.), a very small deposit of glittering white needles, m. p. 210°, was obtained in close vicinity to the solid, and an evil-smelling dirty yellow oil was deposited in small amount on the cooled receiver.

(c) *In neutral solution.* Experiment (a) was repeated using a mixture of 36% formaldehyde (30 g.) and water (90 ml.). After some hours a clear, colourless oil was formed below the aqueous phase. This was separated, but could not be purified by distillation, even at very low pressures, as extensive decomposition took place with the production of a golden-yellow, stinking, involatile oil. Analyses were therefore made on the impure product (Found: Se, 73·2%).

Chlorination of Trimethylene Triselenide.—(a) *With chlorine.* Dry chlorine was passed into a well-stirred suspension of trimethylene triselenide in anhydrous carbon tetrachloride, cooled in a freezing mixture. Initially the suspension appeared to thicken and then the white solid became yellow and dissolved, leaving a gummy deposit including red selenium. Much heat was evolved at this stage and the carbon tetrachloride layer became deep yellow. Further chlorination caused a darkening of this colour to a deep red. The course of this reaction could not be adequately followed by weighing owing to the considerable side reactions, but the colour of the carbon tetrachloride layer was a good index of the extent of chlorination. Chlorination was stopped at the desired stage, the mixture filtered, and the bulk of the carbon tetrachloride distilled off at atmospheric pressure. The residual oil was fractionally distilled in an all-glass apparatus at 1—2 mm. The table gives the results of three typical experiments.

$(CH_2Se)_3$, g.	Colour of CCl_4 layer.	Pale yellow fraction, b. p. 39—42°/2 mm., g.	Dark red fraction, b. p. 44—50°/1·5 mm., g.	Intermediate fraction, g.	Deep yellow fraction, b. p. 96—100°/1·5 mm., g.
133	Reddish-yellow	none	24·0	17	22·0
148	Deep red	none	80·0	none	none
85	Deep yellow	7·7	none	12·0	28·1

In all cases the temperature rose very slowly between fractions. Careful redistillation gave three products of constant b. p.: (i) *Bischloromethyl selenide*, a pale yellow mobile liquid, b. p. 42°/2 mm. (Found: Se, 44·1; Cl, 40·1; C, 13·3; H, 2·1%; *M* (cryoscopic in C_6H_6), 180. $C_2H_4Cl_2Se$ requires Se, 44·4; Cl, 39·8; C, 13·4; H, 2·2%; *M*, 178·2). (ii) *Chloromethylselenenyl chloride*, a dark red heavy oil, b. p. 52°/1·5 mm. A fairly pure sample could be obtained by rapid distillation of the substance with excess of chlorinating agent through a very short column [Found: Se, 48·0; Cl, 41·9%; *M* (cryoscopic in C_6H_6), 195. CH_2Cl_2Se requires Se, 48·2; Cl, 43·2%; *M*, 164]. (iii) *Bischloromethyl diselenide*, a golden-yellow, heavy oil, b. p. 97°/1·5 mm. (Found: Se, 60·9; Cl, 27·2; C, 10·0; H, 2·4%; *M* (ebullioscopic in C_6H_6), 258. $C_2H_4Cl_2Se_2$ requires Se, 61·5; Cl, 27·6; C, 9·3; H, 1·6%; *M*, 256·4].

(b) *With selenium monochloride.* As in the chlorinations with chlorine, the products depended on the relative proportions of the reactants. Two typical experiments are therefore described.

(i) Finely divided trimethylene triselenide (15 g.) was shaken for 30 minutes with selenium monochloride (34 g.) dissolved in anhydrous carbon tetrachloride (50 ml.). On filtration and removal of the solvent a dark red oil was obtained. This, on fractional distillation, gave a heavy red liquid (8 g.), b. p. 52°/1·5 mm., identical in properties and analysis with chloromethylselenenyl chloride obtained in (a).

(ii) Use of trimethylene triselenide (60 g.) and selenium monochloride (70 g.) and fractionation gave a light-yellow liquid (5 g.), b. p. 43°/2 mm., and a golden-yellow oil (12 g.), b. p. 96°/1·5 mm., identical with the bischloromethyl selenide and diselenide previously obtained.

Hydrolysis of Bischloromethyl Selenide.—Several grams of bischloromethyl selenide were refluxed with a 1% aqueous solution of borax. On passage of the vapours evolved into an alcoholic solution of dimedon and into a solution of 2 : 4-dinitrophenylhydrazine in dilute hydrochloric acid, crystalline derivatives were obtained. These on recrystallisation gave m. p.s 186° and 164° respectively, which correspond with the m. p.s of the derivatives formed by formaldehyde with these two reagents. A white solid, which was also formed by the treatment with borax, was washed free from boric acid with warm water, and dried. Preliminary examination showed that it was almost undoubtedly trimethylene triselenide. It was, therefore, refluxed with concentrated hydrochloric acid to convert it into the

high-melting form, washed with water, and thoroughly dried. Recrystallisation gave colourless white needles, m. p. 200° (Found : Se, 83·5. Calc. for $C_2H_4Se_4$: Se, 83·0%).

A similar hydrolysis was carried out quantitatively, using 0·7% aqueous sodium hydrogen carbonate in place of borax. A 70% yield of trimethylene triselenide, based on the selenium taken, was obtained and practically the whole of the chlorine was recovered from the aqueous phase.

Hydrolysis of Chloromethylselenenyl Chloride.—Chloromethylselenenyl chloride (10 g.) was thoroughly shaken with distilled water (200 ml.), a golden yellow oil contaminated with a little red selenium being formed. This was extracted with carbon tetrachloride and on fractional distillation of this extract 5 g. of an oil, b. p. 96°/1·5 mm., were obtained (Found : Se, 61·0. Calc. for $C_2H_4Cl_2Se_2$: Se, 61·5%). Evaporation of the supernatant aqueous layer gave a sticky yellowish-white solid which was not amenable to investigation.

Treatment of Bischloromethyl Diselenide with Potassium Cyanide.—To a solution of the diselenide (10 g.) in acetone was added, with constant stirring, potassium cyanide (2·5 g.) dissolved in methyl alcohol. The buff-coloured precipitate which formed was then filtered off and the major portion of the solvent was removed by evaporation under reduced pressure on a water-bath. The evil-smelling, sticky syrup thus obtained was treated with a fresh portion of acetone and the insoluble material filtered off. This consisted mainly of potassium selenocyanate. Fractional distillation of the filtrate gave a light-yellow liquid (1·5 g.), b. p. 178°/760 mm., identified as bischloromethyl selenide by refluxing it with zinc dust in ethyl alcohol. A white solid was obtained, which, on recrystallisation from nitrobenzene gave colourless needle-shaped crystals, m. p. 173°, identical (m. p. and mixed m. p.) with the crystals obtained by a similar treatment of a sample of the bischloromethyl selenide obtained from the chlorination experiments.

Analytical Procedures.—Selenium. A weighed quantity of the substance was placed in an all-glass distillation apparatus fitted with a tap funnel. Several ml. of saturated aqueous silver nitrate were added and the mixture was gently warmed. Reaction then occurred with the formation of black silver selenide and nitrous fumes. When this reaction appeared to be complete, 100 ml. of concentrated hydrobromic acid were added from the tap funnel and the bulk of this acid was then slowly distilled, the condenser being vertical, with its open end dipping just below the surface of a little hydrobromic acid. The selenium in the distillate, present as selenium tetrabromide, was precipitated by treatment with sulphur dioxide until the first appearance of colloidal red selenium, the reduction then being completed by the addition of several g. of hydroxylamine hydrochloride and boiling. The precipitated selenium was separated in the usual manner and weighed.

Halogens. Halogen was determined by the modified Dains method (*J. Amer. Chem. Soc.*, 1920, **42**, 1574) described by Ives, Pittman, and Wardlaw (*J.*, 1947, 1080). This was further modified, however, removal of selenium by boiling with dilute sulphuric acid being replaced by reduction with sulphur dioxide, followed by filtration.

Carbon and hydrogen were determined by Drs. Weiler and Strauss, Oxford.

Action of Potassium Iodide and Iodine Monochloride on Selenium Compounds.—The technique used was that described by McCullough, Campbell, and Krilanovich (*Ind. Eng. Chem., Anal.*, 1946, **18**, 638).

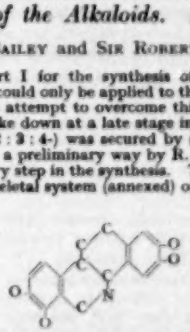
Birkbeck College, London, E.C.4. [*Received, March 2nd*, 1950.]

282. *Synthetical Experiments in the Chelidonine–Sanguinarine Group of the Alkaloids. Part II.*

By A. S. Bailey and Sir Robert Robinson.

The method described in Part I for the synthesis of substituted benzphenanthridines related to the sanguinarine group could only be applied to the preparation of 4 : 5-disubstituted catechol ethers of the series. An attempt to overcome this disability by blocking a reactive position with a bromine atom broke down at a late stage in the process.

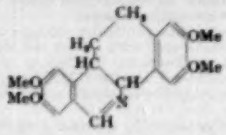
The required orientation (1 : 2 : 3 : 4-) was secured by starting with opianic acid, a route which has already been studied in a preliminary way by R. D. Haworth and abandoned owing to the failure to achieve a necessary step in the synthesis. This difficulty has been surmounted and a derivative possessing the skeletal system (annexed) of the natural alkaloids of the group has been obtained.

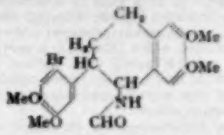


A summary of the results has already been published (*Nature*, 1949, **164**, 402), and a preliminary announcement has also been made in collaboration with R. S. Staunton (*Nature*, 1950, **165**, 235) of the conversion of the end-product described in this communication into a reference compound obtained by Späth and Kuffner (*Ber.*, 1931, **64**, 2034) from both sanguinarine and chelerythrine.

Part I of this investigation (Richardson, Robinson, and Seijo, *J.*, 1937, 835) included an account of the preparation of a tetramethoxytetrahydro-1 : 2-benzphenanthridine (I), the

last stage being the cyclisation of a substituted formamide. In resuming the research we proposed to apply this method to the brominated derivative (II) with the object of inducing

(I.) 

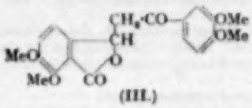
 (II.)

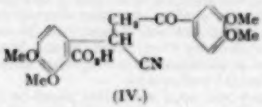
ring-closure in the *ortho*-position to methoxyl, and so to obtain the orientation of the catechol nuclei which occurs in all the known alkaloids of the group. The substance (II) was prepared by following the methods of Part I (cf. the Experimental section) but cyclodehydration could not be brought about, despite many trials.

It occurred to us that a series of reactions similar to those of Part I (but also differing in some obvious respects) might well be based on the use of opianic acid instead of veratraldehyde as the starting point, and this scheme would automatically ensure the correct orientation of catechol nuclei.

After working on this project for some months we found that R. D. Haworth (*J.*, 1937, 1312) had initiated work on the same lines and abandoned it because of the failure of the stage of addition of the elements of hydrogen cyanide. In our experience too, this proved extremely troublesome and the idea was set aside for a time.

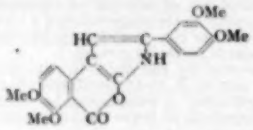
Fortunately the difficulty was eventually surmounted by the use of special conditions, which must be strictly observed.

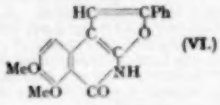

(III.)


(IV.)

6 : 7-Dimethoxy-3-(3 : 4-dimethoxyphenacyl)phthalide (III) (Haworth, *loc. cit.*) was treated with potassium cyanide in 2-methoxyethanol solution at 100°, in the presence of sodium acetate, to form β-(3 : 4-dimethoxybenzoyl)-α-(2-carboxy-3 : 4-dimethoxyphenyl)propionitrile (IV). On treatment with alkaline hydrogen peroxide the related amide was obtained, and this could be further hydrolysed by hot alkali to the dibasic acid (IV; CN ⟶ CO_2H).

Another route to the same substance starts with the dehydration of (IV) by heat, or by treatment with hot hydrochloric acid in acetic acid. This produces a yellow compound, $C_{11}H_{10}O_6N$, believed to be (V); on hydrolysis with hot aqueous sodium hydroxide, the above dibasic acid is obtained. Haworth (*loc. cit.*) obtained a similar yellow substance from 6 : 7-di-

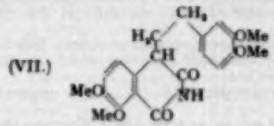
(V.) 

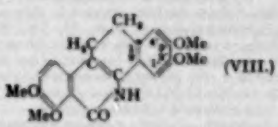
 (VI.)

methoxy-3-phenacylphthalide (Goldschmidt, *Monatsh.*, 1891, **12**, 476) by the action of potassium cyanide (intermediate not characterised) followed by concentrated hydrochloric acid at 100°. He considered the product to be a furan derivative (VI). We prefer the transposition of O and NH, as in (V) because the lactone structure provides a better explanation of the ease of hydrolysis. 2-Pyridones are notably difficult to hydrolyse by means of alkalis. Moreover the experiments of Rogers (*J.*, 1943, 590; B.P. 544,101), Rogers and Davies (*J.*, 1944, 126), and Knott (*J.*, 1947, 1196) exemplify the ready conversion of β-acylpropionitriles into pyrrole derivatives. There can be little doubt but that (V) is the dimethoxy-derivative of Haworth's substance, $C_{10}H_{11}O_4N$, and yet the behaviour on alkaline hydrolysis of the two is different. Haworth (*loc. cit.*) obtained an alkali-soluble substance in colourless prisms, m. p. 184—185° (decomp.) (Found: C, 61·3; H, 5·0. Calc. for $C_{10}H_{12}O_5$: C, 61·0; H, 5·1. Calc. for $C_{11}H_{14}O_7$: C, 61·4; H, 4·8. Calc. for $C_{10}H_{14}O_6$: C, 61·0; H, 4·8%).

The keto-dibasic acid (IV; CN in place of CO_2H) was reduced by Clemmensen's method

to γ-(3 : 4-dimethoxyphenyl)-α-(2-carboxy-3 : 4-dimethoxyphenyl)butyric acid which is readily converted into its imide (VII). This homophthalimide derivative was found to be convertible in good yield into 7 : 8 : 2′ : 3′-tetramethoxy-3 : 4-dihydro-1 : 2-benzphenanthridone (VIII) by the action of a mixture of phosphoric anhydride and glacial phosphoric acid. Many other methods were tried with much inferior results.


(VII.)


(VIII.)

Various attempts have been made to transform the anhydrocryptopine structure into that of sanguinarine type, but up to the present without success, probably because the vinyl group is reactive at the α- and not at the β-position.

Experimental.

3 : 4-*Dimethoxyphenyl* 2-*Bromo*-4 : 5-*dimethoxystyryl Ketone*.—2N-Sodium hydroxide (120 c.c.) was added to a solution of 6-bromoveratraldehyde (110 g.) and acetoveratrone (85 g.) in boiling ethanol (1000 c.c.). A yellow solid separated almost immediately and next day this was collected, washed with alcohol, and dried; it had m. p. 160—163° (120 g., 66%). 3 : 4-*Dimethoxyphenyl* 2-*bromo*-4 : 5-*dimethoxystyryl ketone* crystallised from acetone as stout, pale yellow rods, m. p. 165—166° (Found: C, 55·8; H, 4·5. $C_{18}H_{19}O_5Br$ requires C, 56·1; H, 4·7%). The 2 : 4-*dinitrophenylhydrazone* separated from xylene in red, woolly needles, m. p. 240—242° (Found: N, 9·8. $C_{24}H_{23}O_8N_4Br$ requires N, 9·6%).

β-(3 : 4-*Dimethoxybenzoyl*)-α-(2-*bromo*-4 : 5-*dimethoxyphenyl*)*propionitrile*.—The addition of hydrogen cyanide to the unsaturated ketone could not be accomplished either by an adaptation of the method given in *Org. Synth.*, 1930, **10**, 80, or by Richardson, Robinson, and Seijo's method (*loc. cit.*).

A solution of the above chalkone (41 g.) in boiling 2-methoxyethanol (150 c.c.) and glacial acetic acid (6 g.) was heated in boiling water and stirred mechanically, and sodium cyanide (11 g.) in water (25 c.c.) added dropwise during 5 minutes. The solid, at first precipitated, disappeared after 5 minutes and a white solid soon began to separate. Ten minutes after all the cyanide had been added the boiling water-bath was removed, water (75 c.c.) added, and the solution allowed to cool slowly to room temperature and then placed in the refrigerator. Next day the solid was collected, washed with water, and dried; it had m. p. 167—169° (42 g., 96%). β-(3 : 4-*Dimethoxybenzoyl*)-α-(2-*bromo*-4 : 5-*dimethoxyphenyl*)*propionitrile* crystallised from acetone in colourless, hard prisms, m. p. 170—171° (Found: C, 55·6; H, 4·3; Br, 18·8. $C_{20}H_{20}O_5NBr$ requires C, 55·3; H, 4·6; Br, 18·4%).

β-(3 : 4-*Dimethoxybenzoyl*)-α-(2-*bromo*-4 : 5-*dimethoxyphenyl*)*propionamide*.—Concentrated sulphuric acid (35 c.c.) was gradually added during 15 minutes to the stirred suspension of the nitrile (43 g.) in acetic acid (300 c.c.). After 15 minutes the solution was poured into water (1·5 l.) and the solid *amide* collected (43 g.; m. p. 176—178°) was pure enough for the next stage. Crystallised from ethanol and then from ethyl acetate, it formed colourless rhombs, m. p. 186—187° (Found: N, 2·9. $C_{20}H_{22}O_6NBr$ requires N, 3·1%).

β-(3 : 4-*Dimethoxybenzoyl*)-α-(2-*bromo*-4 : 5-*dimethoxyphenyl*)*propionic Acid*.—A solution of the above mentioned amide (43 g.) in ethanol (300 c.c.), along with 2N-sodium hydroxide solution (300 c.c.), was refluxed until evolution of ammonia ceased (13—15 hours). Most of the alcohol was distilled off and water (300 c.c.) and excess of 5N-hydrochloric acid were added to the filtered liquid. The solid (36·1 g., 80%) which separated was crystallised from alcohol, and β-(3 : 4-*dimethoxybenzoyl*)-α-(2-*bromo*-4 : 5-*dimethoxyphenyl*)*propionic acid* so obtained in colourless prisms which melted partly at 160—164°, resolidified, and remelted at 174—175° (Found: C, 53·2; H, 4·7; Br, 17·2. $C_{20}H_{21}O_7Br$ requires C, 53·0; H, 4·6; Br, 17·7%).

1-*Keto*-6 : 7-*dimethoxy*-2-(2-*bromo*-4 : 5-*dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—A mixture of (dimethoxybenzoyl)(bromodimethoxyphenyl)propionic acid (45 g.), amalgamated zinc (150 g.), water (75 c.c.), glacial acetic acid (5 c.c.), concentrated hydrochloric acid (150 c.c.), and toluene (250 c.c.) was refluxed for 48 hours, concentrated hydrochloric acid (25 c.c.) being added every 12 hours. After cooling, the toluene layer was washed with water, and then extracted with 2N-sodium carbonate solution (3 × 40 c.c.). The combined extracts were boiled and acidified with dilute hydrochloric acid. The oil that separated became a glass when cold, and this was soluble in organic solvents but could not be crystallised. A small quantity of the substance was distilled (b. p. 200°/0·01 mm.), yielding again an uncrystallisable glass.

The crude product, dried by heating at 100° *in vacuo* for an hour, was refluxed with phosphoryl chloride (150 c.c.) for 5 minutes; the resulting dark green solution was cooled and then poured on ice. A gum separated which rapidly solidified. Next day the solid was collected, washed well with water, and crystallised from methanol; it had m. p. 135—137° (34·8 g., 84% calc. on the keto-acid). 1-*Keto*-6 : 7-*dimethoxy*-2-(2-*bromo*-4 : 5-*dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydronaphthalene* was obtained in colourless plates, m. p. 138—139° after recrystallisation (Found: C, 57·4; H, 5·2; Br, 18·4. $C_{20}H_{21}O_5Br$ requires C, 57·1; H, 5·0; Br, 19·0%). The 2 : 4-*dinitrophenylhydrazone* crystallised from dioxan as clusters of red, prismatic needles, m. p. 254—256° (Found: N, 9·3. $C_{32}H_{33}O_8N_4Br$ requires N, 9·4%). The *oxime* (prepared in pyridine) crystallised from methanol in colourless prisms which lost solvent at 120° and then had m. p. 158—159° (Found: N, 3·5. $C_{20}H_{22}O_5NBr$ requires N, 3·2%).

1-*Formamido*-6 : 7-*dimethoxy*-2-(2-*bromo*-4 : 5-*dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydronaphthalene* (II).—The foregoing ketone (5 g.) and formamide (25 c.c.) were heated together for an hour at 160°. Ammonium sulphate (2 g.) was added and the mixture heated for 4 hours at 180—190° (oil-bath). The warm mixture was poured into ice-water, the solid which separated was extracted with chloroform, the chloroform extract washed with water, dried (Na_2SO_4), and the solvent removed. The residual oil was boiled with methanol (10 c.c.), and the solid collected, washed with methanol, and dried (2·6 g., 49%). 1-*Formamido*-6 : 7-*dimethoxy*-2-(2-*bromo*-4 : 5-*dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydronaphthalene* crystallised from dioxan–ethanol in fine needles, m. p. 241—243° (Found : C, 55·6; H, 5·4; N, 3·1. $C_{21}H_{24}O_5NBr$ requires C, 56·0; H, 5·3; N, 3·1%).

Attempts to cyclise this amide with phosphoryl chloride alone, or in toluene or xylene, failed. The desired reaction could not be effected by the use of phosphoric anhydride in xylene, or by syrupy phosphoric acid, or by phosphorus pentachloride in chloroform solution.

β-(3 : 4-*Dimethoxybenzoyl*)-α-(2-*carboxy*-3 : 4-*dimethoxyphenyl*)*propionitrile* (IV).—The experimental conditions described below are critical.

6 : 7-Dimethoxy-3-(3 : 4-dimethoxyphenacyl)phthalide (50 g.; m. p. 168—169°; Haworth, *loc. cit.*, gives m. p. 165—167°) was dissolved in boiling 2-methoxyethanol (150 c.c.), and crystallised sodium acetate (20 g.) added; the solution then became yellow. The flask containing the solution was immersed in a boiling water-bath, and potassium cyanide (20 g.) in water (30 c.c.) added during 2 minutes from a funnel, the stem of which reached to the bottom of the flask. The solution was occasionally stirred and after 10 minutes 2N-hydrochloric acid (250 c.c.) was added, and the liquid then seeded and allowed to cool slowly. Next day a few drops of concentrated hydrochloric acid were added and the very pale yellow solid collected, washed, and dried. This material (*A*) was used directly for the next stage (see below). A small quantity was crystallised thrice from methanol and once from ethyl acetate. β-(3 : 4-*Dimethoxybenzoyl*)-α-(2-*carboxy*-3 : 4-*dimethoxyphenyl*)*propionitrile* was thus obtained in clusters of rhombs which become pale yellow at 122°, shrink slightly at 133°, melt at 156—158° with gas evolution, and resolidify to an orange solid which then melts at 229—231° (Found : C, 63·2; H, 5·5. $C_{21}H_{21}O_7N$ requires C, 63·2; H, 5·3%).

The substance is soluble in cold dilute sodium carbonate solution. When a solution of the nitrile in a drop of aqueous ammonia (*d* 0·88) is heated at 100° for 5 minutes a deep-green solution is produced. Also, when heated at 100° in formamide the substance rapidly gives a deep-green solution.

Lactone of 2-*Hydroxy*-5-(3 : 4-*dimethoxyphenyl*)-3-(2-*carboxy*-3 : 4-*dimethoxyphenyl*)*pyrrole* (V).—(*a*) The last-mentioned nitrile was heated in an oil-bath at 140° for half an hour *in vacuo*. Gas was evolved and the orange residue had m. p. 228—230°. Crystallisation from dioxan gave clusters of fine rods, m. p. 234—236° (decomp.) (Found : C, 65·8; H, 5·0; N, 3·2. $C_{21}H_{19}O_6N$ requires C, 66·2; H, 5·0; N, 3·7%).

(*b*) The crude material (*A*) (see above) was dissolved in boiling acetic acid (120 c.c.), the source of heat removed, and concentrated hydrochloric acid (20 c.c.) added. The heat of the reaction caused the deep-red solution to boil, and an orange-red solid began to separate from the solution. After the mixture had been heated for 5 minutes on a steam-bath, warm water (30 c.c.) was added. Next day, the solid was collected, washed with water and with aqueous methanol, and dried, m. p. 227—229° (46 g., 88% on the two stages). Crystallisation from acetic acid and then from dioxan gave the *lactone* in clusters of pale yellow rods, m. p. and mixed m. p. with the product prepared as in (*a*), 234—236°. *X*-Ray powder photographs confirmed the identity of the two specimens (Found : C, 66·3; H, 5·2; N, 3·6%).

The substance is insoluble in cold sodium hydroxide solution and in dilute mineral acid. It forms a deep-red solution in cold concentrated sulphuric acid which becomes brown on warming. With *p*-dimethylaminobenzaldehyde in boiling acetic acid containing a drop of concentrated hydrochloric acid, a deep green colour rapidly developed. The substance was recovered unchanged after being refluxed for 30 minutes with *p*-nitrophenylhydrazine in acetic acid solution.

β-(3 : 4-*Dimethoxybenzoyl*)-α-(2-*carboxy*-3 : 4-*dimethoxyphenyl*)*propionic Acid* (IV; CN in place of CO_2H).—The above lactone (30 g.) was refluxed with 2N-sodium hydroxide (300 c.c.). A dark green solution was formed as the solid slowly dissolved, ammonia was evolved, and the solution gradually became pale yellow. After the evolution of ammonia had ceased (1—2 hours), the filtered liquid was acidified with dilute hydrochloric acid. A gum separated, which rapidly solidified and was collected, washed with water, and crystallised from 90% acetic acid; it had m. p. 192—196° (decomp.) (25 g., 76%). A further 2 g. were recovered from the mother-liquors. Three crystallisations from acetic acid gave β-(3 : 4-*dimethoxybenzoyl*)-α-(2-*carboxy*-3 : 4-*dimethoxyphenyl*)*propionic acid* in colourless rhombs, m. p. 198—200° (decomp.) (Found : C, 60·1; H, 5·3; *M* (cryoscopic in camphor), 420; equiv. (by titration), 218. $C_{21}H_{22}O_8$ requires C, 60·3; H, 5·3%; *M*, 418; equiv., 209).

The acid gave the potentiometric titration curve expected for a dibasic acid. The 2 : 4-*dinitrophenylhydrazone* crystallised from dioxan–ethanol in orange-red prisms, m. p. 225—227° (decomp.) (Found : N, 9·1. $C_{33}H_{32}O_{12}N_4$ requires N, 9·4%).

The acid (1 g.) was refluxed with acetic anhydride (6 c.c.) for 15 minutes. Excess of acetic anhydride was removed *in vacuo* on the steam-bath, and the residue crystallised twice from ethyl acetate containing a trace of acetic anhydride. The *anhydride* formed fine needles, m. p. 167—168° (Found : C, 63·1; H, 4·9. $C_{21}H_{20}O_7$ requires C, 63·0; H, 5·0%), soluble in cold 2N-sodium hydroxide forming a yellow solution.

A suspension of the anhydride (0·3 g.) in 2N-sodium carbonate solution (3 c.c.) was heated on a steam-bath. A yellow solution was formed which became colourless in 5 minutes. Excess of hydrochloric acid was added, and the precipitate collected and crystallised from 90% acetic acid; m. p. and mixed m. p. with the original dibasic acid, 200—202° (decomp.).

β-(3 : 4-*Dimethoxybenzoyl*)-α-(2-*carboxy*-3 : 4-*dimethoxyphenyl*)*propionamide*.—A solution of the above (dimethoxybenzoyl)(carboxydimethoxyphenyl)propionitrile (4 g.) in cold N-sodium hydroxide (10 c.c.) was mixed with aqueous hydrogen peroxide (2 c.c. of 30%) and water (20 c.c.). After 6 hours at room temperature, the mixture was acidified with hydrochloric acid. The solid, which separated, was

collected, washed with water, and crystallised from ethanol. The *amide* formed clusters of fine rods, m. p. 178—180° (decomp.) (Found: C, 60·3; H, 5·7; N, 3·6. $C_{21}H_{23}O_4N$ requires C, 60·8; H, 5·5; N, 3·4%).

A solution of the amide (0·5 g.) in 2*N*-sodium hydroxide (5 c.c.) was heated on a steam-bath until evolution of ammonia ceased (30 minutes). The acid was precipitated with dilute hydrochloric acid and crystallised from acetic acid, m. p. and mixed m. p. 196—198° (decomp.) (Found: C, 59·8; H, 5·2%).

γ-(3 : 4-*Dimethoxyphenyl*)-α-(2-*carboxy*-3 : 4-*dimethoxyphenyl*)*butyric Acid* [*Dibasic Acid related to* (VII)].—A mixture of toluene (300 c.c.), glacial acetic acid (5 c.c.), water (50 c.c.), concentrated hydrochloric acid (150 c.c.), amalgamated zinc (200 g.), and the keto-dibasic acid (50 g.) was refluxed for 60 hours, concentrated hydrochloric acid (50 c.c.) being added every 12 hours. After 12 hours' refluxing most of the keto-acid had disappeared, and after 24 hours a new solid began to separate from the toluene layer. After 60 hours' refluxing the mixture was distilled until approx. 150 c.c. of toluene had been removed, then allowed to cool and the white solid collected, and washed well with water. The zinc residues were extracted with boiling 50% acetic acid (100 c.c.), and the solid also dissolved in this extract. The solution was filtered and cooled; the product, collected and washed with 50% acetic acid, had m. p. 169—170° (38·5 g., 80%). γ-(3 : 4-*Dimethoxyphenyl*)-α-(2-*carboxy*-3 : 4-*dimethoxyphenyl*)*butyric acid* crystallised from 50% acetic acid as colourless, diamond-shaped prisms, m. p. 171—172° (decomp.) [Found: C, 62·4, 62·6; H, 6·0, 5·8; *M* (cryoscopic in camphor), 417. $C_{21}H_{24}O_8$ requires C, 62·4; H, 5·9%; *M*, 404]. Potentiometric titration gave the curve expected for a dibasic acid. The *anhydride*, prepared by refluxing the acid with acetic anhydride, crystallised from ethyl acetate as large rhombs, m. p. 155—156°, soluble in cold 2*N*-sodium hydroxide to a yellow solution (Found: C, 64·8; H, 5·6. $C_{21}H_{22}O_7$ requires C, 65·3; H, 5·7%).

7 : 8-*Dimethoxy*-4-[2-(3 : 4-*dimethoxyphenyl*)*ethyl*]*homophthalimide* (VII).—A solution of (carboxydimethoxyphenyl)(dimethoxyphenyl)butyric acid (10 g.) in aqueous ammonia (15 c.c.; *d* 0·880) was evaporated to dryness *in vacuo* on the steam-bath. Ammonium carbonate (3 g.) was added to the crystalline residue, and the mixture heated for 45 minutes *in vacuo* at 160—170° (oil-bath). The temperature of the bath was then raised to 190—200° for 15 minutes and the resulting pale orange glass crystallised from ethyl acetate, m. p. 126—127° (8·3 g., 87%). The *imide* separated from ethyl acetate as colourless rhombs, m. p. 127—127·5° (Found: C, 65·7; H, 6·1; N, 3·3. $C_{21}H_{23}O_5N$ requires C, 65·6; H, 6·0; N, 3·6%), soluble in cold aqueous sodium hydroxide to a yellow solution.

Heating the methylammonium salt of the acid *in vacuo* gave 7 : 8-*dimethoxy*-N-*methyl*-4-[2-(3 : 4-*dimethoxyphenyl*)*ethyl*]*homophthalimide* as clear, hexagonal prisms [from benzene–light petroleum (b. p. 60—80°)], m. p. 110—111° (Found: C, 65·8; H, 6·2. $C_{22}H_{25}O_5N$ requires C, 66·2; H, 6·3%).

7 : 8 : 2′ : 3′-*Tetramethoxy*-3 : 4-*dihydro*-1 : 2-*benzphenanthridone* (VIII).—(*a*) The above homophthalimide (1 g.), finely powdered, was slowly added to 10 c.c. of sulphuric acid (4 vols. of concentrated acid, 1 vol. water). The resulting deep-red solution was left at the room temperature for 40 hours and then poured on ice, and the mixture shaken with chloroform. The chloroform extract was washed with sodium carbonate solution and water and then dried (Na_2SO_4), and the solvent removed. Crystallisation of the residue from dioxan and then from chloroform–ethanol gave a small quantity (*ca.* 100 mg.) of a pale yellow solid, m. p. 257—259° (decomp.), not depressed by admixture with the substance prepared as below.

(*b*) Phosphoric anhydride (40 g.) was stirred with syrupy phosphoric acid (100 c.c.), and the above homophthalimide (20 g.) (finely powdered) was added to the hot solution. The mixture was then heated at 120° (oil-bath) for an hour, cooled, and poured on ice. A yellow gum separated and this became solid in a few minutes on trituration at *ca.* 90°. The washed product was crystallised from pyridine, giving 14·6 g. (77%) of a pale yellow solid, m. p. 254—257°. 7 : 8 : 2′ : 3′-*Tetramethoxy*-3 : 4-*dihydro*-1 : 2-*benzphenanthridone* was very sparingly soluble in the usual organic solvents, except chloroform and acetic acid. It crystallised from *n*-butanol (100 vols.) as long, cream-coloured needles, m. p. 260—262° (decomp.) (Found: C, 68·4; 68·6; H, 5·8, 5·8; N, 3·8. $C_{21}H_{21}O_5N$ requires C, 68·7; H, 5·7; N, 3·8%). The substance is insoluble in dilute acids; it dissolves in concentrated sulphuric acid to a red solution, and in concentrated hydrochloric acid to a yellow solution. It gives a green colour with ferric chloride in alcoholic solution.

The *perchlorate* crystallised from acetic acid containing perchloric acid as yellow clusters of rods, m. p. 219—221° (decomp.) (Found: C, 53·5; H, 4·8; N, 2·4. $C_{21}H_{21}O_5N,HClO_4$ requires C, 53·9; H, 4·7; N, 3·0%). The salt was decomposed by water, regenerating the phenanthridone.

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283. 4-*Hydroxy*cyclo*hexane*-1-*carboxylic Acid*.

By N. R. CAMPBELL and J. H. HUNT.

The form of 4-hydroxy*cyclo*hexane-1-carboxylic acid hitherto assigned the *trans*-configuration is shown to contain both the *cis*- and the *trans*-isomer. The authentic *trans*-acid has been prepared, and also the previously unknown *cis*-4-acetoxy*cyclo*hexanecarboxylic acid.

4-HYDROXY*CYCLO*HEXANE-1-CARBOXYLIC ACID (I) was first prepared, by reduction of 4-keto*cyclo*hexane-1-carboxylic acid with sodium amalgam, by W. H. Perkin, jun. (*J.*, 1904, **85**, 416), who described it as a solid of melting point 120—121°. Since distillation yielded a product which was completely soluble in sodium carbonate solution, this material was assumed to have

the *trans*-configuration. The same acid has been made more recently by Hardegger, Plattner, and Blank (*Helv. Chim. Acta*, 1944, **27**, 793), using essentially the same method; they record m. p. 119—120° and also assume that the product has the *trans*-configuration.

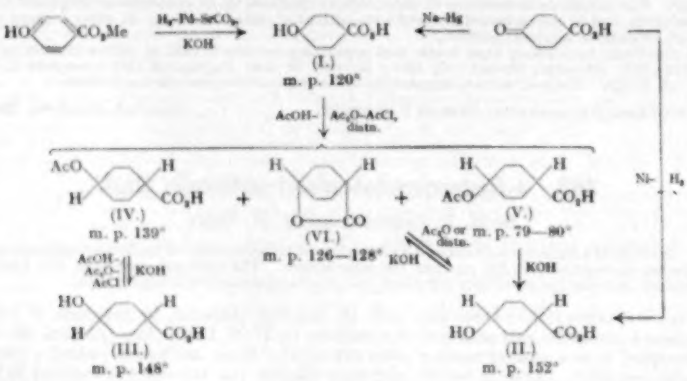
Martin and Robinson (*J.*, 1943, 497), who prepared 4-hydroxy*cyclo*hexane-1-carboxylic acid by hydrolysis of the ester obtained by hydrogenation of ethyl *p*-hydroxybenzoate, state that the pure *trans*-acid melts at 121°. This method was also used, with slight modification, by Hardegger, Heusser, and Blank (*Helv. Chim. Acta*, 1946, **29**, 477), who did not record the melting point of their product.

Balaš and Šrol (*Coll. Trav. Chim. Czech.*, 1929, **1**, 658), by hydrogenation of *p*-hydroxybenzoic acid, obtained an acid melting at 152°, which readily lactonised on distillation and was accordingly assumed to be the *cis*-isomer (II). They also obtained a small quantity of the acid melting at 119—120°. This work has been repeated by Owen and Robins (*J.*, 1949, 326), who also obtained, as a principal product, the acid of m. p. 152°.

On repeating the work of Hardegger, Plattner, and Blank (*loc. cit.*) we obtained the acid (I), m. p. 119—120°, which gave a 44% yield of the acetoxy-acid (IV), m. p. 139°. Hardegger *et al.* (*loc. cit.*) had obtained this acid in 50% yield, with the same melting point.

The aqueous mother-liquors from the recrystallisation of the acetoxy-acid were saturated with ammonium sulphate and the separated oil distilled. The product, which was equivalent to a yield of 42% of acetoxy-acid, deposited a small quantity of crystalline material, which, after exhaustive recrystallisation from chloroform and from ethyl acetate, melted at 148°. The acid value and ultimate analysis indicated that this was a hydroxy*cyclo*hexanecarboxylic acid, which was initially assumed to be identical with the *cis*-acid described by Balaš and Šrol (*loc. cit.*). However, when it was acetylated, the product proved to be, not the expected lactone, but an acid which melted at 139° and did not depress the melting point of the acetoxy-acid (IV). Hydrolysis of (IV) gave a hydroxy-acid which showed no depression of melting point on admixture with the new hydroxy-acid (m. p. 148°). A 50% mixture of the new hydroxy-acid with an authentic specimen of the known *cis*-acid (Hardegger *et al.*, *loc. cit.*) melted over the range 119—134°, but, after resolidifying, the mixture melted at 118—120° and after recrystallisation from ethyl acetate still melted at 120°, not depressing the melting point of the hydroxy-acid (I) hitherto regarded as the *trans*-isomer. It was then found that mixtures of the new hydroxy-acid with 40—60% of the authentic *cis*-acid melt within the range 118—121°.

The new hydroxy-acid distilled virtually unchanged at atmospheric pressure, no lactone being formed. Under these conditions, the *cis*-acid readily lactonises (Balaš and Šrol, *loc. cit.*). On distillation the hydroxy-acid (I) gave a first fraction containing mostly the lactone (VI) derived from the *cis*-acid (II), and a later, acidic fraction which was largely unsaturated but from which it was possible to isolate a small quantity of the new hydroxy-acid, m. p. 148°. That the small yield of the new hydroxy-acid may have been caused by dehydration under the conditions of rather prolonged heating was indicated by the preparation, from the unsaturated fraction, of a dibromo-acid melting at 84°, which was evidently 3 : 4-dibromo*cyclo*hexanecarboxylic acid (cf. Perkin, *J.*, 1904, **85**, 433).



It is evident that the hydroxy-acid of m. p. 148° is the authentic *trans*-4-hydroxy*cyclo*hexane-1-carboxylic acid (III) and that the previously accepted *trans*-acid (I), m. p. 120°, contains both isomers, probably in equal proportions. The latter conclusion is confirmed by the fact that the hydroxy-acid (I) gives no more than 50% of pure acetoxy-acid. We have repeated the work of Hardegger, Heusser, and Blank (*loc. cit.*), who claimed a 75% yield of acetoxy-acid, of unstated m. p., from a specimen of hydroxy-acid, presumably (I); we obtained a 79% yield of crude crystalline material (m. p. 102—118°), but no more than 46% of the pure acetoxy-acid (IV).

Further treatment of the oil, from which the new *trans*-hydroxy-acid had been separated, yielded a small quantity of a lactone (VI), m. p. 127—128° (cf. Hardegger, Plattner, and Blank, *loc. cit.*), together with an acetoxy*cyclo*hexanecarboxylic acid of m. p. 79—80°. Hydrolysis of both the lactone and the new acetoxy-acid yielded the *cis*-hydroxy-acid (II) (mixed m. p.). Accordingly, the new acetoxy-acid must be the hitherto unknown *cis*-4-acetoxy-acid (V).

These results throw light on observations by Owen and Robins (*loc. cit.*). These authors assumed the *trans*-configuration for the hydroxy-acid (I), melting at 120°, and have shown that the solid product obtained by Perkin (*loc. cit.*) by distillation of that acid was the lactone (VI), which may also be obtained from the pure *cis*-acid; they supposed this to be evidence of inversion under the conditions of experiment. Furthermore, they report that on Bouveault–Blanc reduction of the ethyl ester of the supposed *trans*-hydroxy-acid (I) a mixture of stereoisomeric glycols was obtained, partial inversion being again invoked. Our results make these assumptions no longer necessary, since Owen and Robins's starting material contained both isomers.

Balaš and Šrol (*loc. cit.*) found the melting point of the lactone obtained by distillation of the pure *cis*-hydroxy-acid (II) to be 100—110° and Owen and Robins (*loc. cit.*) found that of the lactone obtained similarly from the supposed *trans*-hydroxy-acid (I) to be between 108° and 112°, with no alteration on recrystallisation from ether. Hardegger, Plattner, and Blank (*loc. cit.*), however, found the lactone prepared by dehydration of the *cis*-hydroxy-acid (II) under acetylating conditions to melt at 128°. Specimens of the lactone have been obtained by us by all of the above methods, as well as by treating the hydroxy-acid (I) with a mixture of acetic acid, acetic anhydride, and acetyl chloride. In a Thiele tube they all melted between 126° and 128° and exhibited no mutual depression of the melting point. However, further investigation showed that, on very much slower heating, melting occurred over the range 123—128° and alterations in appearance were observed during the cooling of the melts. Since these phenomena persisted after repeated recrystallisation from different solvents and after sublimation, the presence of polymorphic forms was suspected. Dilatometry indicated changes between 83° and 87° and between 126° and 129°. Thermal analysis showed that the lower transition temperature was 84—85°, corresponding, apparently, to a change in crystal structure. The higher transition, the melting-point, was 127—129°. No evidence was obtained for any change between 108° and 112°, in purified specimens of the lactone (VI).

Experimental.

4-*Hydroxy*cyclo*hexane*-1-*carboxylic Acid* (I) (*m. p.* 120°).—This was prepared from 4-keto*cyclo*hexane-1-carboxylic acid by reduction with sodium amalgam (Hardegger, Plattner, and Blank, *loc. cit.*) and by hydrolysis of the product obtained by hydrogenation of methyl *p*-hydroxybenzoate at 150°/130 atm. using palladium on strontium carbonate (Robinson *et al.*, *loc. cit.*, and Hardegger, Heusser, and Blank, *loc. cit.*). The products appeared to be identical.

trans-4-*Acetoxy*cyclo*hexanecarboxylic Acid* (IV).—4-Hydroxy*cyclo*hexane-1-carboxylic acid (I) (60 g.) was refluxed for 4 hours with acetic acid (460 ml.), acetic anhydride (46 ml.), and acetyl chloride (4·6 ml.). Excess of the reagents was distilled off under reduced pressure and the residual oil recrystallised several times from water, yielding the required acetoxy-acid (34 g.), m. p. 139° (Hardegger, Plattner, and Blank, *loc. cit.*) (Found: C, 58·3; H, 7·6. Calc. for $C_9H_{14}O_4$: C, 58·05; H, 7·6%).

trans-4-*Hydroxy*cyclo*hexane*-1-*carboxylic Acid* (III).—(*a*) The aqueous mother-liquors from the preparation of the above acetoxy-acid were saturated with ammonium sulphate and extracted with ether. The oil remaining after evaporation of the ether was distilled, a fraction being collected boiling at 146—152°/0·4 mm. (32 g.). The distillate deposited a small amount of crystalline material, which was collected and washed with carbon tetrachloride. The crude *product* (2·3 g.) had m. p. 131°, raised to 148° by three recrystallisations from chloroform and one from ethyl acetate (Found: C, 58·0; H, 8·3; acid value, 396. $C_7H_{12}O_3$ requires C, 58·3; H, 8·4%; acid value, 390). The mixed m. p. with *cis*-4-hydroxy*cyclo*hexane-1-carboxylic acid (II) (m. p. 152°) (Balaš and Šrol, *loc. cit.*) was 119—134°.

(*b*) The acetoxy-acid (IV) (0·5 g.) was hydrolysed by being kept overnight with 20% potassium hydroxide solution (10 ml.)). The mixture was then acidified (Congo-red) with dilute sulphuric acid and extracted with ethyl acetate. The extract was dried ($MgSO_4$) and evaporated, yielding crystals (0·3 g.) which on recrystallisation from ethyl acetate had m. p. 149°, not depressed on admixture with the hydroxy-acid (III) obtained as described under (*a*).

Reacetylation of the Hydroxy-acid (III).—Under the conditions described above this gave an almost quantitative yield of the acetoxy-acid (IV), m. p. 139° after one recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°).

Distillation of the Hydroxy-acid (III).—When distilled, (III) (20 mg.) gave an oil which completely solidified and had m. p. 139°. Recrystallisation from ethyl acetate raised the m. p. to 147°, unchanged on admixture with the original hydroxy-acid (III).

cis-4-*Acetoxy*cyclo*hexanecarboxylic Acid* (V).—The oil remaining after separation of the hydroxy-acid (III) in the preparation (*a*) above failed to crystallise and was hydrolysed by heating on the water-bath with 10% potassium hydroxide solution for 2 hours. The crude acid (26 g.; m. p. 112°) extracted from the acidified solution was reacetylated under the same conditions as before and the product distilled. The distillate (24 g.; m. p. 60—90°) was dissolved in ether and extracted with potassium hydrogen carbonate solution. The ethereal solution (*A*) was reserved for further treatment and the aqueous extract acidified. Next morning a small quantity of crystalline material had been deposited, having m. p. 50—60°, raised to 139° after three recrystallisations from water. This gave no depression of the m. p. of the *trans*-acetoxy-acid (IV). The aqueous mother-liquors were extracted with ether, and the sticky product so obtained was crystallised from water. The m. p. (53°) of this crude product was unaffected by further crystallisation from water, but separation was effected by fractional crystallisation from *cyclo*hexane. By recrystallisation from ethyl acetate–light petroleum (b. p. 40—60°) the tail fraction yielded cis-4-*acetoxy*cyclo*hexanecarboxylic acid*, m. p. 79—80° (Found: C, 58·1; H, 7·4. $C_9H_{14}O_4$ requires: C, 58·05; H, 7·6%).

Methyl cis-4-*acetoxy*cyclo*hexanecarboxylate*, prepared by diazomethane, had b. p. 83°/0·7 mm., n_D^{20} 1·4539 (Found: C, 59·7; H, 8·0. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·0%).

cis-4-*Hydroxy*cyclo*hexane*-1-*carboxylic Acid Lactone* (VI).—The ethereal solution (*A*) of the neutral products above was evaporated, yielding a syrup which crystallised on storage. The crystals melted at 117—126°, raised to 126—128° on recrystallisation from light petroleum (b. p. 40—60°). This substance caused no depression of the m. p. of the lactone prepared from *cis*-4-hydroxy*cyclo*hexane-1-carboxylic acid (II) (Balaš and Šrol, and Hardegger *et al.*, *locc. cit.*) (Found: C, 66·9; H, 8·0. Calc. for $C_7H_{10}O_2$: C, 66·7; H, 8·0%). Thermal and dilatometric analyses of the lactone were carried out by standard methods. The lactone used was recrystallised once from ether and twice from light petroleum (b. p. 40—60°), and finally sublimed in a high vacuum. When slowly heated the substance shrank and sintered at 123°, and then rapidly melted at 126·5° and cleared at 128°. On cooling, crystallisation commenced sharply at 126·5° and the appearance of the crystal mass changed at 71·5°. Owing to the solubility of the lactone in most organic liquids, near to its melting point, mercury was used, in a dilatometer having an upturned bulb.

cis-4-*Hydroxy*cyclo*hexane*-1-*carboxylic Acid* (II).—(*a*) 4-Keto*cyclo*hexane-1-carboxylic acid was reduced in sodium hydroxide solution by shaking it with hydrogen in the presence of Raney nickel (Hardegger, Plattner, and Blank, *loc. cit.*). The purified product, as reported, had m. p. 152° and on distillation (Balaš and Šrol, *loc. cit.*) or on heating with acetic anhydride (Hardegger *et al.*), yielded identical lactones, m. p. 126—128°. This acid was assumed to be the authentic *cis*-4-hydroxy*cyclo*hexane-1-carboxylic acid.

(*b*) *cis*-4-Acetoxy*cyclo*hexanecarboxylic acid (V) (0·5 g.) was hydrolysed by being kept for 16 hours at room temperature with 20% potassium hydroxide solution (10 ml.). The mixture was extracted once with ether (rejected) and acidified with dilute sulphuric acid (Congo-red). Extraction with ethyl acetate yielded on evaporation an acid, m. p. 144—150°, raised to 152° after two recrystallisations from ethyl acetate (Found: C, 58·8; H, 8·3. Calc. for $C_7H_{10}O_3$: C, 58·3; H, 8·4%). The m. p. was unchanged on admixture of the substance with the authentic *cis*-hydroxy-acid, prepared as described under (*a*).

(*c*) The lactone (VI), hydrolysed under the same conditions as above, yielded *cis*-4-hydroxy*cyclo*hexane-1-carboxylic acid (II), m. p. 152°.

Distillation of 4-*Hydroxy*cyclo*hexane*-1-*carboxylic Acid* (I).—Distillation of this acid at atmospheric pressure yielded a fraction, b. p. 260°, which solidified, and a second, oily fraction boiling between 290° and 350°. The total distillate was dissolved in ether, and the acidic substances were extracted with 10% potassium hydrogen carbonate solution. Evaporation of the ethereal solution yielded *cis*-4-hydroxy-*cyclo*hexane-1-carboxylic acid lactone (0·76 g.), m. p. 100—110°, raised to 126—128° on recrystallisation from light petroleum (b. p. 40—60°) and from ether. The aqueous extract, after acidification with dilute sulphuric acid, was extracted twice with ether and thrice with ethyl acetate. The former extract, on evaporation, yielded an oil (0·74 g.), which decolorised a solution of bromine in carbon tetrachloride. The ethyl acetate extract gave a small yield of crude *trans*-4-hydroxy*cyclo*hexane-1-carboxylic acid (0·13 g.), m. p. 140—144°, raised to 147° on recrystallisation from ethyl acetate. A dibromo-acid, prepared from the unsaturated fraction in carbon tetrachloride, melted at 84° (Perkin, *loc. cit.*, gives m. p. 86° for 3 : 4-dibromo*cyclo*hexanecarboxylic acid).

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284. *Reactions of Iodine Monohalides in Different Solvents.*

By F. W. Bennett and A. G. Sharpe.

The course of the reaction between iodine monochloride and phenols varies with experimental conditions: in the absence of a solvent the main reaction is chlorination; in solution it is iodination. Iodine monobromide always acts as a brominating agent. The relation between such reactions and the physical properties of the solvents and reactants is discussed.

It has been recognised for some time that there is a connection between the dielectric constant of a solvent and the type of reaction that usually occurs in it (Hughes and Ingold, *J.*, 1935, 244; Waters, *J.*, 1942, 153; *idem*, "The Chemistry of Free Radicals," Oxford, 1946). Solvents of high dielectric constant favour heterolytic, those of low dielectric constant homolytic, fission of bonds; gaseous reactions nearly always involve homolytic fission. There is, however, a scarcity of examples of the course of a reaction varying steadily as the dielectric constant of the medium is increased.

The interaction of iodine monochloride and salicylic acid affords such an example. The main reaction between the solid acid and iodine monochloride vapour, which is only 0·4% dissociated at 25°, is one of chlorination; in carbon tetrachloride ($\varepsilon = 2{\cdot}2$) iodination predominates; and in nitrobenzene ($\varepsilon = 36$) iodination takes place exclusively. The course of the reaction between iodine monochloride and phenol varies in a similar way.

The effect of a solvent on the polarity of the I–Cl bond was discussed by Fairbrother (*J.*, 1936, 847), who found the dipole moment of iodine monochloride to be 0·8 D. in the vapour phase and 1·5 D. in carbon tetrachloride. From the first ionisation potential of iodine (10·44 e.v.) and the electron affinity of chlorine (3·75 e.v.) he calculated that dissociation of an ICl molecule into infinitely separated I^+ and Cl^- ions requires 6·69 e.v. (*i.e.*, 155 kcals.mol.$^{-1}$) more energy than dissociation into atoms. When the bond breaks during reaction in the absence of a solvent, atoms rather than ions will thus result, and the observed reaction with phenols is the expected one.

Fairbrother also estimated the magnitude of the difference between the two dissociation energies in various solvents and concluded that in a solvent of dielectric constant greater than 3·9 free ions should be formed; a feeble conductivity in chlorobenzene ($\varepsilon = 5{\cdot}8$) was observed. In carbon tetrachloride, the preponderance of iodination when an electron-donating group (OH) is present in the organic molecule indicates that the main reaction involves heterolytic fission of the I–Cl bond. In acetic acid ($\varepsilon = 7{\cdot}1$) and nitrobenzene iodine monochloride yields conducting solutions (Sandonnini and Borghello, *Atti R. Accad. Lincei*, 1937, **25**, 46; Bruner and Galecki, *Z. physikal. Chem.*, 1913, **84**, 513) and in these solvents, in which free ions are present before reaction, iodination alone occurs. Mr. N. Greenwood has recently shown that iodine monochloride in carbon tetrachloride is a non-conductor.

It was pointed out by Gillam and Morton (*Proc. Roy. Soc.*, 1929, *A*, **124**, 610; 1931, *A*, **132**, 154) that solutions of iodine monochloride in solvents of low dielectric constant are usually brown, whilst those in solvents of higher dielectric constant are yellow. A further illustration of the effect of the solvent has been found in the reaction between iodine monochloride and silver perchlorate: in carbon tetrachloride precipitation of silver chloride is exceedingly slow, whilst in nitrobenzene formation of a precipitate is instantaneous, and after four hours is quantitative.

Although iodine monochloride (usually in acetic acid) is widely used for the iodination of phenols and amines, Militzer (*J. Amer. Chem. Soc.*, 1938, **60**, 256) found that in carbon tetrachloride or acetic acid iodine monobromide functions only as a brominating agent. It has now been found that even in nitrobenzene, in which the bromide forms conducting solutions (Bruner and Galecki, *loc. cit.*), the reaction with phenol or salicylic acid is still one of bromination.

Several factors enter into the explanation of this. The electron affinity of bromine (3·56 e.v.) is less than that of chlorine and formation of ions from gaseous atoms would therefore absorb more energy than the corresponding process for the chloride. The energy of solvation of the bromide ion ($r = 1{\cdot}95$ A.) will be less than that of the chloride ion ($r = 1{\cdot}81$ A.) in the same solvent (Webb, *J. Amer. Chem. Soc.*, 1926, **48**, 2589). Iodine bromide is dissociated into free halogens to a much greater extent than iodine monochloride. Bromination by bromine is a much faster process than iodination by the I^+ ion.

The free-energy changes attending the reactions

$$IBr_{(in\ CCl_4)} \rightleftharpoons \tfrac{1}{2}I_{2\,(in\ CCl_4)} + \tfrac{1}{2}Br_{2\,(in\ CCl_4)}\ (\Delta G = 1{\cdot}75\ \text{kcals.})$$

and

$$ICl_{(in\ CCl_4)} \rightleftharpoons \tfrac{1}{2}I_{2\,(in\ CCl_4)} + \tfrac{1}{2}Cl_{2\,(in\ CCl_4)}\ (\Delta G = 4{\cdot}02\ \text{kcals.})$$

have been determined by Yost, Anderson, and Skoog (*ibid.*, 1933, **55**, 552) and Blair and Yost (*ibid.*, p. 4489). Since no change in the number of molecules is involved, the degree of dissociation is independent of the concentration; it is 9·5% for the bromide and 0·25% for the chloride. Thermodynamic data for solutions in other solvents are unfortunately not available, but there is no reason to believe that iodine bromide will not always be dissociated into its elements to a much greater extent than iodine monochloride.

In a solution of a phenol and iodine bromide in nitrobenzene, free bromine and I^+ ions will therefore compete for the phenol. Since the bromination of a phenol by bromine is a very fast reaction, whereas iodination by the iodine cation is relatively slow (see, *e.g.*, Lambourne and Robertson, *J.*, 1947, 1167) the resultant reaction is iodine-catalysed bromination, and iodine may be recovered at the end of the reaction.

Experimental.

Materials.—Iodine monochloride was prepared and purified by the method of Cornog and Karges (*Inorg. Synth.*, Vol. I, p. 165). Iodine bromide was made by warming together the theoretical proportions of the elements. Silver perchlorate, obtained according to Hill (*J. Amer. Chem. Soc.*, 1921, **43**, 254) was analysed by precipitation of the silver as chloride (Found: Ag, 51·7. Calc. for $AgClO_4$: Ag, 52·0%). Carbon tetrachloride was dried by distillation; nitrobenzene was dried ($CaCl_2$) and distilled. The phenol and salicylic acid were free from halogen-containing impurities. Soda-lime used for decomposition of organic materials contained a trace of chloride; this was determined and a small correction for halide thus introduced was made and has been incorporated in the results quoted below.

Interaction of Iodine Monochloride and Salicylic Acid.—Iodine monochloride (11·6 g.) and salicylic acid (5·0 g.) were allowed to react in solution in carbon tetrachloride or nitrobenzene, or in the absence of a solvent. In absence of a solvent a large amount of iodine was rapidly liberated on the surface of the salicylic acid; in carbon tetrachloride a little iodine was liberated, and in nitrobenzene no free iodine was detected even by shaking the reaction mixture with starch solution.

After 24 hours, by which time about half of the original oxidising power had disappeared, the reaction mixture was shaken with sodium hydrogen sulphite solution (to remove iodine or unchanged iodine monochloride) and then with aqueous sodium hydroxide. The aqueous extract was separated from the organic solvent and acidified with hydrochloric acid; salicylic acid (unchanged) and its substitution products were extracted with ether. The ethereal extracts were combined and evaporated to dryness, and the product was kept in a desiccator over silica gel for a week. Since the object of the experiment was to identify the type of substitution, no attempt to separate the mixture of organic acids was made. The mixture was finely powdered and thoroughly mixed, and relatively large samples (*ca.* 1 g.) were decomposed by heating them at a red heat with a measured large excess of soda-lime. The product was dissolved in dilute nitric acid and treated with a known excess of 0·1*N*-silver nitrate; the silver halides were filtered off and weighed, and the silver remaining in solution was precipitated and weighed as chloride. In addition to this quantitative analysis, qualitative analyses were made on the organic products obtained from both salicylic acid and phenol. Results with phenol and iodine monochloride were qualitatively similar to those obtained with salicylic acid.

The product from interaction in absence of a solvent always contained a considerable quantity of chlorine and less iodine; the silver halide precipitate contained 62·4% of Ag (Calc. for AgCl: Ag, 72·3. Calc. for AgI: Ag, 45·9%). This corresponds to a chlorine : iodine ratio in the products of approximately 2 : 1; chlorination is therefore the main reaction.

From carbon tetrachloride solution the product always contained iodine and a little chlorine; the introduction of the chlorine agreed with the observed slight liberation of iodine. The silver halide precipitate contained 52·7% of silver, corresponding to an approximate chlorine : iodine ratio of 1 : 12.

The product from the reaction in nitrobenzene was free from chlorine; the silver halide precipitate contained 46·4% of silver. In one experiment in glacial acetic acid the result was qualitatively similar to that in nitrobenzene; no iodine was liberated during the reaction between iodine monochloride and salicylic acid.

Interaction of Iodine Monochloride and Silver Perchlorate.—When silver perchlorate, dissolved in a little benzene, was added to iodine monochloride in carbon tetrachloride no precipitate appeared for several minutes. When the mixture was kept, a precipitate of silver chloride was produced. In nitrobenzene the appearance of a precipitate was immediate, and within four hours precipitation was complete and no silver remained in solution. By use of equivalent amounts of iodine monochloride and silver perchlorate, the weight of precipitate obtained after filtration in a Gooch crucible and drying at 120° corresponded to a silver content of 72·6%. The reaction may therefore be represented by the equation: $ICl + AgClO_4 = AgCl + IClO_4$.

Reactions of Iodine Bromide.—Militzer's experiments with iodine bromide (*J. Amer. Chem. Soc.*, 1938, **60**, 256) were repeated with nitrobenzene as solvent and phenol and salicylic acid as substances to be halogenated. The organic products contained no more than a trace of iodine. At the end of the brisk reaction between iodine bromide and phenol a large quantity of iodine was precipitated and thiosulphate titration showed that 54% of the original oxidising power remained.

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University Chemical Laboratory, Cambridge. [*Received, March 4th*, 1950.]

285. *Reactions of α-Cyanoprene (1-Cyanobuta-1 : 3-diene). Part III. Dimers.*

By (Mrs.) J. L. Charlish and W. H. Davies.

α-Cyanoprene (1-cyanobuta-1 : 3-diene), on storage at low temperatures in acetic acid, gives a dimer, *cis*-1-cyano-2-*trans*-2′-cyanovinylcyclohex-5-ene, the structure of which is confirmed by hydrogenation and hydrolysis to the known saturated diacid. When heated, this dimer is converted into the 2-*cis*-β-cyanovinyl isomer. On treatment with bases these isomers give another pair of isomers, 1-cyano-2-2′-cyanoethylidenecyclohex-5-enes.

In recent publications, Snyder and his co-workers (*J. Amer. Chem. Soc.*, 1949, **71**, 1055, 1057, 1395) reported the separation of the *cis*- and the *trans*-form of α-cyanoprene (1-cyanobuta-1 : 3-diene) and examined their reactions. One form, probably the *trans*-form, dimerised to give a 1-cyano-2-(2′-cyanovinyl)*cyclo*hexene. This structure was proved by bromination followed by dehydrohalogenation, the resulting nitrile being hydrolysed to the known β-(2-carboxyphenyl)-propionic acid. We also have investigated the properties of this dimer and have found its detailed structure by a different method. We find also that the dimer reported by Snyder—which will be referred to as dimer A—is readily converted into isomeric forms, dimers B, C, and D.

The carbon skeleton was elucidated by hydrogenating dimer A to its tetrahydro-derivative which was hydrolysed to give the known *cis*- and *trans*-β-(2-carboxy*cyclo*hexyl)propionic acids (Windaus, Hückel, and Reverey, *Ber.*, 1923, **56**, 91): *cis*-diacid, m. p. 103—105° (dianilide, m. p. 179°), and *trans*-diacid, m. p. 143—145° (dianilide, m. p. 213°). Windaus *et al.* (*loc. cit.*) give m. p. 103° and 143° for the *cis*- and *trans*-β-(2-carboxy*cyclo*hexyl)propionic acids, and m. p. 159° and 212° for the *cis*- and *trans*-dianilides, respectively, though no method of preparation and no analysis is given for the *cis*-dianilide. In view of the alternative proof of structure of cyanoprene dimer given by Snyder and Poos, there can be no doubt that the diacids obtained are indeed β-(2-carboxy*cyclo*hexyl)propionic acids; Windaus's m. p. 159° instead of 179° for the *cis*-dianilide may be a typographical error.

Hückel (*Z. angew. Chem.*, 1926, **39**, 842) reported hydrolysis of esters of *cis*-β-(2-carboxy-*cyclo*hexyl)propionic acid with sodium ethoxide to the *trans*-acid. In agreement with this, the tetrahydro-nitrile with aqueous alkali gave complex mixtures, presumably of the *cis*- and *trans*-derivatives, from which the only diacid isolated was the *trans*-form; besides this, an acid amide was readily separated. Acid hydrolysis, on the other hand, gave simpler products and pure *cis*- and *trans*-acids were obtained in good yield by hydrolysing pure compounds (the dicyanide and the acid amide, respectively). It follows that under the conditions used (100°), hydrochloric acid does not rapidly convert one acid into the other and it is, therefore, probable that the tetrahydro-dimer is in the *cis*-configuration. At higher temperatures (180°) with hydrochloric acid, *cis*-β-(2-carboxy*cyclo*hexyl)propionic acid is known to be converted into the *trans*-acid (Windaus *et al.*, *loc. cit.*).

Our dimer A, obtained from aged acetic acid solutions of α-cyanoprene and crystallised from ether, had m. p. 53—54°, and was apparently identical with that of Snyder and Poos. Slow fractional distillation of the ethereal mother-liquors gave an unidentified colourless mobile liquid, b. p. 70—71°/15 mm. (presumably a constant-boiling mixture), and an oil which by crystallisation from ether gave dimer B, m. p. 51·5—53°. When, on the other hand, the total crude oil (after removal of α-cyanoprene) was slowly distilled, only dimer B was obtained, but rapid distillation gave a mixture of dimers A and B from which the pure products were separated with difficulty. Prolonged heating caused considerable formation of non-volatile resin. It therefore appears that dimer A is present in the crude α-cyanoprene residues and that it is converted by heat into dimer B.

Attempts were made to add 2-nitropropane to each of the dimers, using methyltriethyl-ammonium hydroxide as catalyst, though it was known that alkali alone caused their rapid polymerisation. The only products isolated were isomers of the starting materials, dimer A giving dimer C, m. p. 70—71°, and dimer B giving dimer D, m. p. 86—88°. The same isomerisation was effected with morpholine and is presumably promoted by basic catalysts. An attempt was made to convert dimer C into dimer D by heating it at 150°, but from the resinous product no pure component was isolated. The inter-relations of the dimers are summarised below:

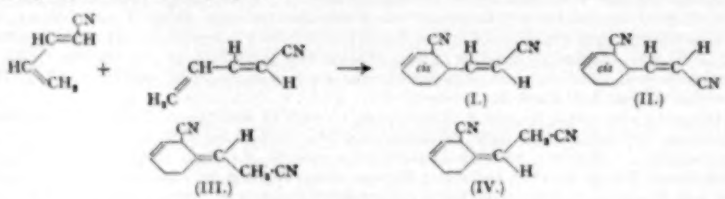
Dimer C, m. p. 70—71° ← (base) Dimer A, m. p. 53—54° → (heat) Dimer B, m. p. 51·5—53·5° → (base) Dimer D, m. p. 86—88°.

Hydrogenation of the four dimers gave the respective tetrahydro-derivatives, all of which gave the same acid-amide after hydrolysis with sodium hydroxide, so that all are 1-cyano-2-2′-cyanoethylcyclohexanes. Dimers A and B gave the same tetrahydro-derivative in quantitative yield and free from stereoisomers; thus it is probable that the double bonds were all of the type $-CH{:}CH-$. Acid hydrolysis of tetrahydro-dimer AB, under conditions milder than those known to cause conversion of *cis*-β-(2-carboxycyclohexyl)propionic acid into its *trans*-isomer (cf. Windaus *et al.*, *loc. cit.*), gave the *cis*-diacid in good yield, thus showing that tetrahydro-dimer AB has the *cis*-configuration. Hence, if hydrogenation had affected only bonds of the type $-CH{:}CH-$, dimers A and B must also have the *cis*-configuration about the cyclohexane ring. Hydrogenation of dimers C and D, on the other hand, gave a mixture of tetrahydro-derivatives, presumably *cis* and *trans* with respect to the cyclohexane ring. It is therefore probable that dimers C and D differ from A and B by the shift of a double bond from $-CH{:}CH{\cdot}CH<$ to $-CH_2{\cdot}CH{:}C<$, in which the quaternary carbon atom is part of the cyclohexane ring.

The position of the double bonds was then investigated. The ultra-violet absorption spectra showed only end absorption, down to 210 mμ. ($E^{1\%}_{1cm.}$ 750—900), whereas α-cyanoprene itself had a maximum at 241 mμ. ($E^{1\%}_{1cm.}$ 2260); therefore, none of the dimers has conjugated double-bonds. Linstead and his co-workers (*J.*, 1927, 2566; 1929, 2139; 1932, 443) have shown that a compound with a double bond βγ to a cyano-group adds iodine chloride more readily than does the isomer with the double bond in the αβ-position; a typical result is 56% addition to a βγ-double bond compared with 3% to an αβ-double bond. Titrations of the four dimers with iodine chloride under standard conditions gave the following mole-% absorption: A 74, B 57, C 105, D 99%. This indicated that a double bond which is αβ to the cyano-group in dimers A and B has migrated to the βγ-position in dimers C and D; it is also probable that the other double bond is βγ to a cyano-group in all four isomers, though the γδ-position is not excluded. The only cyanopropenes which are mainly in the βγ-form on equilibration under alkaline conditions are those which are γγ-dialkyl-substituted (cf. Linstead's table quoted in Gilman's "Organic Chemistry," 2nd edn., p. 1042). It follows then that the conversion of dimers A and B under basic conditions into dimers C and D involves the change $>CH{\cdot}CH{:}CH{\cdot}CN$ to $>C{:}CH{\cdot}CH_2{\cdot}CN$. This cyano-group must be that on the side chain; if it were that on the ring, dimers A and B, as substituted 1-cyanocyclohexenes, would not be expected to give the single isomer on hydrogenation.

Summarising, we see that (i) the four isomers have the same carbon skeleton, (ii) dimers A and B have the same configuration (*cis*) on the cyclohexene ring, (iii) none of the isomers contains conjugated double bonds, (iv) dimers A and B probably have one double bond αβ and the other βγ to cyano-groups, whereas dimers C and D probably have both double bonds βγ to cyano-groups, and (v) the conversion of dimers A and B into dimers C and D under basic conditions involves isomerisation in the side chain of $>CH{\cdot}CH{:}CH{\cdot}CN$ to $>C{:}CH{\cdot}CH_2{\cdot}CN$.

Snyder *et al.* (*loc. cit.*) showed that of the *cis*- and *trans*-forms of α-cyanoprene, one underwent the Diels–Alder reaction, and also dimerised, much more easily than the other, and that from steric considerations the *trans*-isomer would be the more active. The simplest dimer obtained by a Diels–Alder reaction of *trans*-α-cyanoprene with the γδ-bond of a second molecule would be 1-cyano-2-*trans*-2′-cyanovinylcyclohex-5-ene. As dimer A gives a *cis*(ring)-tetrahydro-derivative, dimer A is probably cis-1-*cyano*-2-trans-2′-*cyanovinyl*cyclo*hex*-5-*ene* (I), which agrees with its known properties.



The conversion of dimer A into dimer B by heat does not involve a change in orientation on the cyclohexene ring as these dimers give the same *cis*-tetrahydro-derivative. Nor is it likely to involve migration of double bonds, for Letch and Linstead (*J.*, 1932, 443) have shown that the αβ- and βγ-forms of olefinic cyanides are not equilibrated by heat in the absence of a catalyst. The most probable difference between dimers A and B is, therefore, the geometrical

configuration in the side-chain double bond, so that dimer B is cis-1-*cyano*-2-cis-2'-*cyanovinyl*cyclo*hex*-5-*ene* (II).

In confirmation of this, the dipole moments of dimers A and B were measured by Mr. G. F. Longster, who also calculated the moments of structures (I) and (II). It will be appreciated that the calculated values are only approximate and have to span the values allowing both for the four possible ways in which a *cyclo*hexene ring can crumple and for the free rotation about the single bonds in the side chain. In (I), the cyano-groups tend to reinforce one another, giving a dipole moment of about 5·5 D.; in (II), the groups are to some extent in opposition so that a total moment below that of a single cyano-vector (3·2 D.) is probable. The dipole moments found for dimers A and B were 5·8 and 2·9 D., respectively.

From the discussion above, it is clear that dimers C and D are (III) and (IV), respectively. If this is so, the geometrical configuration of the αβ-unsaturated form governs, to some extent at least, the configuration of the βγ-isomer derived from it. So far as we are aware, this point does not appear to have been examined in the classical studies of cyanopropene tautomerism. Dipole moment measurements and calculations, although in agreement with the proposed formulæ, do not make it possible to decide which dimer is (III), and which (IV).

In conclusion, we should point out that the four dimers obtained in this work were those most easily isolated from reactions under particular conditions and it may well be that in each case other isomers were also present.

Experimental.

Isolation of Dimer A.—The material used was a 50% solution in acetic acid of α-cyanoprene prepared by pyrolysis of the acetate of crotonaldehyde cyanohydrin (Gudgeon and Hill, B.P. 515,737). The solution was stabilised with quinol and had been kept in an ice-house for 6 years.

The solution (5 l.) was shaken with crushed ice and sufficient 16% aqueous sodium hydroxide for neutralisation (about 3 l.). Brine was added and the aqueous layer discarded. The oil was washed twice with water, dried, and distilled under nitrogen (bath-temperature, <80°), to give α-cyanoprene (940 g.), b. p. 36—37°/14 mm. The residual oil (1600 g.) in ether (1 l.) was cooled to −70°; the solid was collected and recrystallised from ether with good cooling to give *dimer A*, cis-1-*cyano*-2-trans-2'-*cyanovinyl*cyclo*hex*-5-*ene* (I) (360 g.). Repeated crystallisation raised the m. p. to 53—54° (Found: C, 75·9; H, 6·1; N, 18·0%; *M*, 164. $C_{12}H_{14}N_2$ requires C, 76·0; H, 6·3; N, 17·7%; *M*, 158).

Dimer B.—The first ethereal mother-liquors from dimer A were slowly fractionated through a good column to give fractions: (*a*) b. p. 38—71°/17 mm. (95 g.), (*b*) b. p. 70—72°/17 mm. (232 g.), (*c*) b. p. 32—118°/0·2 mm. (101 g.), (*d*) b. p. 118—130°/0·13 mm. (262 g.), (*e*) b. p. 130—144°/0·2 mm. (150 g.), and a considerable amount of resin.

Fraction (*b*) was refractionated to give a colourless mobile oil, probably a constant-boiling mixture, b. p. 70—71°/15 mm., n_D^{20} 1·4240 (Found: C, 54·2, 53·8; H, 5·2, 5·2; N, 13·8, 14·2, 14·4%; *M*, 161).

Fraction (*d*) partly solidified on cooling and was twice crystallised from ether to give *dimer B*, cis-1-*cyano*-2-cis-2'-*cyanovinyl*cyclo*hex*-5-*ene*, m. p. 51·5—53·5° (mixed m. p. with dimer A, 26—39°) (Found: C, 75·7; H, 6·35; N, 17·7%; *M*, 156).

Fraction (*e*) had m. p. about 10° and analysed for a cyanoprene polymer (Found: C, 76·2; H, 6·4; N, 18·05%).

In another experiment, the total crude oil after fractionation of the cyanoprene was distilled rapidly under nitrogen. The amount of residual tar was much higher, indicating further polymerisation. The fraction of b. p. 115—130°/0·1 mm. was crystallised from ether to give a solid, m. p. 33—40°, from which dimers A and B were isolated by repeated crystallisations from ether. Slow distillation of the total crude oil through a good column increased the resin formation considerably, but from the distillate pure dimer B was readily isolated and there was no evidence of the presence of dimer A.

Dimer C.—(*a*) A solution of dimer A (16 g.) in dioxan (25 c.c.) was added slowly to a mixture of 2-nitropropane (8·6 g.), 35% aqueous methyltriethylammonium hydroxide (6 c.c.), and dioxan (20 c.c.) at 40°. After being heated for 1 hour at 70°, the cooled mixture was acidified with 2N-hydrochloric acid and extracted with ether. The extract was dried, the solvent removed, and the residue crystallised from alcohol with good cooling (−10°), to give *dimer C* (1-*cyano*-2-2'-*cyanoisohylidene*cyclo*hex*-5-*ene*) m. p. 70—71° (Found: C, 75·8; H, 6·2; N, 17·75%; *M*, 164). When the 2-nitropropane was omitted in this reaction, only viscous polymers were obtained.

(*b*) A solution of dimer A (2·0 g.) and morpholine (2·0 c.c.) in alcohol (8 c.c.) was kept for 4 days, poured into water, and acidified with 2N-hydrochloric acid. The oil was extracted with ether and dried, the solvent removed, and the residue crystallised from alcohol, to give dimer C, m.p. and mixed with that obtained by (*a*), 70—71°.

Dimer D.—(*a*) Dimer B was treated with 2-nitropropane in the same way as dimer *A* (see previous section) to give *dimer D* (1-*cyano*-2-2'-*cyanoisohylidene*cyclo*hex*-5-*ene*), m. p. 86—88° (from alcohol) (Found: C, 75·6; H, 6·4; N, 17·3%; *M*, 161). (*b*) Dimer B was treated with morpholine in the same way as dimer A (see previous section) to give dimer D, m. p. and mixed m. p. with product obtained above, 86—88°.

Hydrogenation of Dimers.—(*a*) Dimer A (4 g.) in methyl alcohol (20 c.c.) was hydrogenated at room temperature and pressure over a pre-reduced catalyst from 0·15 g. of 7·8% palladium-on-calcium-carbonate in methyl alcohol (10 c.c.). Hydrogen absorption was 1160 c.c. (Calc. for 2 double bonds in $C_{12}H_{18}N_2$, 1134 c.c.) The rate of absorption fell rapidly after 600 c.c. had been absorbed. The mixture was filtered and the bulk of the solvent distilled off. The residue was poured into water and extracted with ether, the extract dried, and the solvent removed, to give *tetrahydro-dimer AB*, cis-1-*cyano*-2-2'-

cyanoethylcyclohexane, m. p. 32—33·5° (m. p. not raised by crystallisation from methyl alcohol) (Found: C, 74·1; H, 8·7; N, 16·95. $C_{10}H_{14}N_2$ requires C, 74·1; H, 8·6; N, 17·3%).

(*b*) Dimer B was hydrogenated under the same conditions to give tetrahydro-dimer AB, m. p. 32—33·5°, identical with that from dimer A.

(*c*) Dimer C was hydrogenated under the same conditions (hydrogen absorbed: 1115 c.c.) to give *tetrahydro-dimer C* (a mixture of *cis*- and *trans*-1-*cyano*-2-2′-*cyanoethylcyclohexane*) as a viscous oil, b. p. 112—119°/0·2 mm., which partly solidified on strong cooling (Found: C, 74·2; H, 8·4%).

(*d*) Dimer D was hydrogenated under the same conditions (hydrogen absorption: 1120 c.c.) to give *tetrahydro-dimer D* as a viscous oil, b. p. 103—110°/0·075 mm., which partly solidified on strong cooling (Found: C, 74·3; H, 8·0%).

The curves for the rates of hydrogenation for dimers B, C, and D were almost identical: for dimer A, the uptake of the first mole of hydrogen was more rapid.

Hydrolysis of Tetrahydro-dimer AB.—(a) *With acid.* The tetrahydro-dimer (11·2 g.) was refluxed for 20 hours with a mixture of 35% hydrochloric acid (25 c.c.) and water (25 c.c.), a further 22 c.c. of acid being added after 3 hours' heating. After cooling, crystals separated and were collected (m. p. 86—94°). Repeated crystallisation from water gave *cis*-β-(2-carboxy*cyclo*hexyl)propionic acid, m. p. 103—104° (Found: C, 59·85; H, 8·15%; equiv., 100·7. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·0%; equiv., 100). The acid (1 g.) in thionyl chloride (0·8 c.c.) was kept overnight. After removal of excess of thionyl chloride at 30°/15 mm., ether (5 c.c.) was added and the solution treated with aniline (2·5 c.c.) in ether (5 c.c.). The mixture was stirred with water and acidified with hydrochloric acid. The solid was collected, washed with dilute sodium hydroxide (m. p. 176—177°), and repeatedly crystallised from methyl alcohol to give the *cis*-dianilide, m. p. 179—180° (Found: C, 75·6; H, 7·35; N, 8·5. $C_{22}H_{26}O_2N_2$ requires C, 75·4; H, 7·4; N, 8·0%). When the acid chloride was prepared by heating the acid with excess of thionyl chloride, only the *trans*-anilide (see below), m. p. 213—214°, was obtained. The methyl ester of the *cis*-acid (prepared by using diazomethane) did not react with aniline below 60°.

(*b*) *With alkali.* Tetrahydro-dimer AB (50 g.) was refluxed for 16 hours with 10% aqueous sodium hydroxide (370 c.c.). The solution, after treatment with carbon, was acidified with hydrochloric acid and the solid collected (43 g.); it had m. p. 160—175°. [The aqueous filtrates were extracted with ether, to yield a viscous oil (13·5 g.) from which no pure product was isolated.] This solid was washed well with ether (for working up of ethereal washings, see below) and repeatedly crystallised from water to give a *half-amide* of *trans*-β-(2-carboxy*cyclo*hexyl)propionic acid (23 g.), m. p. 206—207° (Found: C, 60·45; H, 8·6; N, 6·8. $C_{16}H_{27}O_3N$ requires C, 60·2; H, 8·5; N, 7·0%). The acid amide (1 g.) was refluxed with acetyl chloride (5 c.c.) for 3 hours. The product was washed well with water and crystallised from a large bulk of ether to give the *imide*, m. p. 160—161° (Found: C, 66·25; H, 7·95; N, 7·75. $C_{16}H_{25}O_2N$ requires C, 66·3; H, 8·3; N, 7·7%). The ethereal washings of the crude acid from the hydrolysis were evaporated to small bulk and a little more acid amide was collected. The rest of the ether was then removed and the oily product repeatedly crystallised from benzene to a m. p. of 137—140°. This was not depressed on admixture with the pure *trans*-acid (m. p. 143—145° obtained below).

Hydrolysis of Acid Amide.—(a) *With acid.* The acid amide (1·5 g.) was refluxed with 17% hydrochloric acid (10 c.c.) for 17 hours. After cooling, *trans*-β-(2-carboxy*cyclo*hexyl)propionic acid was collected, having m. p. 143—145°, not altered by repeated crystallisation from water (Found: C, 60·2; H, 8·3. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·0%). The acid (0·5 g.) in aniline (1 c.c.) was refluxed for 2 hours, cooled, and diluted with ether; the solid was collected, washed with aqueous sodium hydroxide, and crystallised from methyl alcohol, to give the *trans*-anilide, m. p. 213—214° (Found: N, 8·4. Calc. for $C_{22}H_{26}O_2N_2$: N, 8·0%).

(b) *With alkali.* The acid amide (1·5 g.) was refluxed with 15% sodium hydroxide (10 c.c.) for 17 hours. The solution, after clarification with carbon, was acidified with hydrochloric acid and extracted with ether. Evaporation of the ether left a mixture of acids, m. p. 105—120°, from which after repeated crystallisation from benzene, a sample of impure *trans*-acid, m. p. 136—138° (clear at 140°), was obtained.

Hydrolysis of Tetrahydro-dimer C.—This tetrahydro-dimer was hydrolysed with sodium hydroxide as described for tetrahydro-dimer AB. The products isolated were the solid amide, m. p. 203—206° (mixed m. p. with authentic sample, 203—207°), and a crude *trans*-diacid, m. p. 136—139° (mixed m. p. with authentic *trans*-diacid, 137—142°).

Hydrolysis of Tetrahydro-dimer D.—This was carried out with sodium hydroxide as described for tetrahydro-dimer AB; the products isolated were the acid amide, m. p. 202—205° (mixed m. p. with authentic sample, 202—206°), and the crude *trans*-diacid, m. p. 135—138° (mixed with authentic *trans*-diacid, 136—140°).

Iodine Chloride Titrations.—The estimations were carried out as described by Letch and Linstead (*J.*, 1932, 443). To obtain reasonable absorption of iodine chloride, the solution of dimer (1/300 mol.) in chloroform was mixed with the alcoholic iodine chloride and kept in the dark for 48 hours. The solution was then poured into aqueous potassium iodide and titrated with 0·1N-sodium thiosulphate. In all cases, a control experiment was done, omitting the addition of the dimer. The results (expressed as % double bond for dimers A, B, C, and D were 74, 57, 105, and 99, respectively.

Dipole Moments (Mr. G. F. Longster).—The dipole moments were determined in benzene as solvent at 25°. The results obtained for dimers A, B, C, and D were 5·8, 2·9, 5·1, and 5·6 D., respectively.

Rough estimates of the dipole moments of structures (I), (II), (III), and (IV) were made by examining molecular models and allowing, so far as possible, for the four crumpled forms of the *cyclo*hexene ring and for the free rotation in the side chain. The results obtained for (I), (II), (III) and (IV) were 5·5, <3·2, >4·2, and 1—5·6 D., respectively.

The authors are grateful to Mr. Longster for his work on the dipole moments.

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286. *Reactions of the Alkyl-sulphate Ion. Part I. Kinetics and Mechanism of the Reaction with Hydroxide Ion.*

By G. H. Green and J. Kenyon.

The bimolecular nature of the reaction between alkyl-sulphate ion and hydroxide ion has been confirmed. When N-aqueous solutions of both reactants are used no concomitant reaction of the alkyl-sulphate ion with neutral water molecules could be observed. The reaction is entirely analogous to the corresponding alkaline hydrolysis of alkyl halides except that, as it takes place between two similarly charged ions and not with an ion and a neutral molecule, its velocity increases with increasing ionic concentration.

In studying the rates of methylation of phenols with sodium methyl sulphate in aqueous alkaline solution (in the press) it was necessary to take into account the simultaneous alkaline hydrolysis of the sodium methyl sulphate which occurs as a side reaction. The kinetic equation derived for the bimolecular methylation reaction with phenol requires the knowledge of the rate constant for the bimolecular second-order hydrolytic reaction under the same experimental conditions. A study was therefore made of the latter reaction.

It is generally recognised that dialkyl sulphates react with hydroxide ions by the bimolecular process :

$$R_2SO_4 + OH^- \longrightarrow RSO_4^- + ROH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

the monoalkyl sulphate formed reacting further but very much more slowly :

$$RSO_4^- + OH^- \longrightarrow SO_4^{--} + ROH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Reaction (1) was investigated by Kremann (*Monatsh.*, 1907, **28**, 13) who, working with diethyl sulphate in heterogeneous aqueous medium with rapid stirring (thus achieving an approximately constant diethyl sulphate concentration in the aqueous phase equal to its solubility), found an approximate proportionality between alkali concentration and speed of hydrolysis. Pollak and Baar (*ibid.*, 1917, **38**, 501) overcame the complication of two separate phases by working in alcoholic solution. However, they based their calculations on a first-order reaction and their value of k consequently fell as the reaction proceeded. Their results are of some value as they show that dimethyl sulphate reacts some 35 times faster than diethyl sulphate, in rough agreement with Kremann who found a ratio of 45 : 1. Klemenc (*ibid.*, p. 353) pointed out that the rate of hydrolysis of dialkyl sulphates by water cannot be neglected in comparison with the rate of hydrolysis by hydroxide ion. On this basis he recalculated Kremann's results and obtained a good constancy of the pseudo-unimolecular rate constant throughout the course of the reaction between diethyl sulphate and alkali.

There is little doubt that this reaction is entirely analogous to that between alkyl halides and hydroxide ion which has been studied in detail by, amongst others, Bateman, Cooper, Hughes, and Ingold (*J.*, 1940, 925) who confirmed the bimolecular mechanism of the reaction between a number of alkyl halides and hydroxide ion in alcoholic solution. The rate of reaction falls rapidly along the homologous series Me > Et > Pr^i owing to increasing accession of electrons on the α-carbon atom. Reaction (1) may be formulated

$$\overset{\delta+}{R}\text{—}CH_2\text{-}O\text{-}SO_2R + OH^- \longrightarrow \left[\begin{matrix} R\text{-}CH_2 \cdots O\text{-}SO_2R \\ | \\ OH \end{matrix}\right]^- \longrightarrow \begin{matrix} R\text{-}CH_2 \\ | \\ OH \end{matrix} + RSO_4^-$$

Reaction (2) has not been studied kinetically. It differs from reaction (1) and the corresponding reaction of alkyl halides in that it is between two negative ions instead of between an ion and a polar molecule. This in itself is sufficient to account for the very great difficulty of hydrolysis of the alkyl sulphate ion as compared with the neutral sulphate.

Experimental.

Metal Alkyl Sulphates.—The method of preparation was based essentially on that given by Cohen ("Practical Organic Chemistry," Macmillan, 1920, p. 50), AnalaR quality reagents being used. The concentrated solution of metal alkyl sulphate was evaporated until crystallisation commenced and the remainder of the water removed *in vacuo* over calcium chloride, sulphuric acid, and finally phosphoric oxide, the anhydrous salt being obtained (cf. Illingworth and Howard, *Phil. Mag.*, 1884, **18**, 123).

Analysis of Metal Alkyl Sulphates.—The metal alkyl sulphates prepared as described above were neutral to phenolphthalein and completely soluble in water to give clear solutions. Traces of carbonate and sulphate were present. These may be removed by recrystallisation from alcohol but large volumes of alcohol are required. Since the carbonate content never exceeded 0·5%, it could be ignored and the total impurities allowed for by quantitative determination of the alkyl sulphate content.

Carbonate was determined by adding 5 ml. of 0·1N-hydrochloric acid to a 1-g. sample and titrating with 0·1N-sodium hydroxide to phenolphthalein.

Alkyl sulphate was determined by hydrolysing a 1·0—1·5-g. sample with 25 ml. of boiling 3N-sulphuric acid under reflux for 3 hours. Under these conditions sodium methyl sulphate is hydrolysed quantitatively, though the higher monoalkyl sulphates require less stringent conditions (Desseigne, *Mem. Serv. Chim. l'Etat*, 1944, **31**, 347). The mixture was cooled and titrated with 0·5N-sodium hydroxide to phenolphthalein. A blank determination was carried out simultaneously. A correction was applied for the acid used by the carbonate present. The analytical results are summarised below.

Preparation.	Na_2CO_3 or K_2CO_3 content, %.	Metal alkyl sulphate content, %.
Sodium methyl sulphate I	0·4	94·8
,, ,, II	0·2	94·1
Potassium methyl sulphate	0·5	91·3
Sodium ethyl sulphate	0·8	93·8

Determination of the Rate of Reaction between Alkyl-sulphate Ion and Hydroxide Ion.—Preliminary experiments showed that the reaction between sodium methyl sulphate and hydroxide ion proceeds at a measurable velocity only at temperatures of the order of 100°. This also applies to the corresponding reaction with phenoxide ion. It was, therefore, most convenient to take the b. p. of water as the temperature of reaction. Since the temperature of boiling water is dependent on atmospheric pressure, to minimise variations in temperature from one experiment to another, all reactions were conducted when the barometric pressure was between 755 and 765 mm. corresponding to a temperature of 100° ±0·2°. To facilitate calculations the experiments were conducted with equimolecular concentrations of metal alkyl sulphate and hydroxide ion :

$$\underset{(a-x)}{RSO_4M} + \underset{(a-x)}{MOH} \longrightarrow \underset{(x)}{ROH} + \underset{(x)}{M_2SO_4}$$

The velocity coefficient k' has been calculated from the usual expression for a second-order reaction, $k' = x/60ta(a - x)$, where t is the time in minutes.

The required amount of anhydrous metal alkyl sulphate was weighed rapidly into a beaker and transferred with carbon dioxide-free water to a graduated flask. The required volume of carbonate-free alkali solution (Note 1) was added by pipette or burette, and the solution made up to volume with carbon dioxide-free water. Aliquots (10 ml.) were pipetted into 6" × 1" test-tubes (Note 2) with widened flanges which enabled the tubes to be supported on a perforated metal sheet. The tubes were closed with rubber stoppers fitted with Bunsen valves. They were then immersed *en masse* into a vigorously boiling water-bath, the level of water in which was maintained by a constant-level device at 1½—2" above the level of the liquid in the tubes. After 10 minutes' heating (zero time) (Note 3) and then at definite intervals tubes were withdrawn and immediately immersed in running cold water. When quite cold the contents of the tubes were titrated with standard 0·5N-hydrochloric acid to phenolphthalein (Note 4).

Note 1 : Carbonate-free sodium hydroxide was prepared according to Britton ("Hydrogen Ions," Chapman and Hall, 1932, p. 32). The carbonate-free potassium hydroxide was prepared by dissolving 64 g. of AnalaR potassium hydroxide pellets in carbon dioxide-free water and making up to 250 ml.

Note 2 : Soft-glass test-tubes were unsatisfactory as after several hours' heating the bottoms tended to drop out. No trouble was encountered with Pyrex or Monax test-tubes. The titre of N-sodium hydroxide remained unchanged in either tube (10-ml. aliquots titrated with 0·5N-hydrochloric acid to phenolphthalein) after 1 hour's heating at 100°, these conditions being more severe than encountered experimentally. Thus any dissolution of the glass by the alkali could be neglected.

Note 3 : A thermometer placed in the reaction mixture indicated that 7—8 minutes were required from the time of immersion of the reaction-tubes in the water-bath for the reaction mixture to attain the maximum temperature.

TABLE I.

Rate of reaction of sodium methyl sulphate with sodium hydroxide in aqueous solution at 100°.

Normality of NaOH = 1·000. Purity of sodium methyl sulphate = 94·8%.

Initial reaction mixture : 4N-NaOH, 62·5 ml.; $CH_3{\cdot}SO_4Na$, 35·36 g. } in 250 ml.

[NaOH] = 1·000; [$CH_3{\cdot}SO_4Na$] = 1·000.

Time (mins.).	Ml. of 0·5N-HCl = residual NaOH.	a.*	$(a - x)$.*	x.*	$10^2k'$.
0	18·4	0·904	—	—	—
20	16·4	0·904	0·806	0·098	11·2
40	14·85	0·904	0·730	0·174	11·0
60	13·4	0·904	0·659	0·245	11·4
80	12·2	0·904	0·601	0·303	11·6
100	11·4	0·904	0·559	0·345	11·4
120	10·5	0·904	0·516	0·388	11·55
150	9·5	0·904	0·467	0·437	11·5
180	8·7	0·904	0·427	0·478	11·5
240	7·5	0·904	0·369	0·535	11·1
				Mean	11·4

* These values have been corrected for the expansion of water from room temperature (20° approx.) to 100°. The true volume of the reaction mixture is 10(1 + 0·000207 × 80) = 10·17 ml.

Note 4 : Measurements at each time interval were carried out usually in duplicate and at zero time usually in triplicate. Only the means are recorded here.

The detailed results of a typical experiment are given in Table I and a summary of the complete results in Table II.

TABLE II.

Second-order rate constants for the reaction between metal alkyl sulphates and hydroxide ion in aqueous solution at 100°.

Expt.	Metal alkyl sulphate.	Initial concn.	Alkali.	Initial concn.	Total ionic concn.*	$10^4k'$.
1A	$CH_3{\cdot}SO_4Na$	0·50	NaOH	0·50	2·00	8·3
1B	$CH_3{\cdot}SO_4Na$	1·00	NaOH	1·00	4·00	11·4
1C	$CH_3{\cdot}SO_4Na$	1·00	NaOH	1·00	4·00	11·3
1D	$CH_3{\cdot}SO_4Na$	1·50	NaOH	1·50	6·00	13·2
2	$CH_3{\cdot}SO_4K$	1·00	KOH	1·00	4·00	11·2
3	$C_2H_5{\cdot}SO_4Na$	1·00	NaOH	1·00	4·00	1·08

* Total ionic concentration = Σ [ion] × charge. This remains constant throughout the reaction. The true ionic concentration is approximately 6% greater than given since the metal alkyl sulphates contained about 6% of impurity calculated as sodium sulphate.

DISCUSSION.

In no experiment was there observed any upward or downward trend of the rate constant. The adherence to second-order kinetics confirms the bimolecular nature of the reactions. It must be pointed out that the results presented here, by themselves, do not prove conclusively that the kinetics of the reaction are of the second order, nor does it follow that because the reaction kinetics are of the second order, the reaction is bimolecular. A satisfactory demonstration would require measurements over a wide range of different concentrations of both alkyl sulphate and hydroxide ion. As stated above, by analogy with the alkaline hydrolysis of the alkyl halides which has been proved conclusively to be bimolecular, the present reaction would be expected to be bimolecular, and the results do support this hypothesis. All reactions were carried to approximately 60% of completion except Expt. 3 (Table II) which went some 20% towards completion. The constancy of the rate constants indicates that any concomitant hydrolysis of the alkyl-sulphate ion by neutral water molecules is either non-existent or negligible. This also applies to the reaction of the corresponding alkyl iodides (Bateman, Cooper, Hughes, and Ingold, *loc. cit.*) but apparently not to the neutral alkyl sulphates (Klemenc, *loc. cit.*).

The substitution of potassium ion for sodium ion does not influence the rate of reaction. Klemenc, however, found that dimethyl sulphate was hydrolysed appreciably faster by potassium hydroxide than by sodium hydroxide which he ascribed to the catalytic influence of the undissociated alkali. The difference in rate decreased with increasing temperature. Differences between the reactivity of sodium and potassium hydroxides have been observed in other reactions, *e.g.*, the reduction of ketones by primary alcohols in the presence of strong alkali (Hargreaves and Owen, *J.*, 1947, 750).

The fall in rate on passing from methyl to ethyl is considerable, the ratio of the rates being 11 : 1. This is in very good agreement with the corresponding ratio for alkyl iodides in 80% aqueous ethanol at 35° of 12·5 : 1 (Bateman, Cooper, Hughes, and Ingold, *loc. cit.*).

There is a marked increase in rate with increasing ionic concentration as expected for a reaction between ions of like charge (Moelwyn-Hughes, " Kinetics of Reaction in Solution," Oxford Univ. Press, 1947, p. 90). It would appear that the low rate of reaction is due principally to the powerful repulsive force between the ions. The change in rate on passing from methyl to ethyl sulphate is probably due only to a change in the activation energy, since the methyl : ethyl ratio is the same as for the neutral alkyl iodides, and the velocities of reaction of the alkyl halides with hydroxide ion agree with the predictions of the simple collision theory, *i.e.*, $P \sim 1$ (Grant and Hinshelwood, *J.*, 1933, 258).

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287. *Studies of Coal Tar Bases. Part III.* By-products of the Hydrogenation of Pyridine with Raney Nickel.*

By J. Idris Jones.

When pyridine is hydrogenated with a Raney nickel catalyst at about 200° or piperidine is heated with the same catalyst in a hydrogen atmosphere at the same temperature, some hydrogenolysis of the piperidine occurs with the formation of high-boiling bases. High yields of hydrogenolysis products are obtained by increasing the temperature. Prominent constituents of the mixture obtained by heating piperidine with the nickel catalyst at 250° are *N*-*n*-butyl-, *N*-*n*-amyl-, and *N*-*cyclo*pentyl-piperidine and 1 : 5-dipiperidinopentane. The *N*-*n*-amylpiperidine was separated from contaminating bases on an ion-exchange column.

Adkins and his co-workers (*J. Amer. Chem. Soc.*, 1934, **56**, 2425) have shown that pyridine and its substituted derivatives are readily hydrogenated in the liquid phase in presence of Raney nickel. An 83% yield of piperidine was obtained after 7 hours at 200° with an unspecified hydrogen pressure (in the range 150—300 atmospheres) and 25 g. of Raney nickel for 610 g. of product. There is no record of the amount of unchanged pyridine or of examination of the distillation residue. The present investigation was initiated after an observation that, even under optimum conditions for pyridine hydrogenation with Raney nickel, a small amount of high-boiling material accompanies the piperidine in the product. By modifying the conditions of the hydrogenation, notably by use of temperatures above 200°, the yield of piperidine drops while the amount of high-boiling material increases. Thus, when pyridine was hydrogenated for 12 hours with 5% of its weight of catalyst at 200°/200 atmospheres 9% of the liquid product obtained distilled above 125°, *i.e.*, well above the boiling point of piperidine or pyridine. At 250°, 300°, and 330°, but under otherwise comparable conditions, the yields of high-boiling product rose to 29, 33, and 45%, respectively. Liberation of ammonia was particularly noticeable at the higher temperatures. In the absence of hydrogen, only 8% of product boiling above 125° was obtained after heating pyridine at 300° for 12 hours with the same amount of Raney nickel. In this case, but not in those noted above, some di-2-pyridyl was identified in the product (cf. Wibaut, *Rec. Trav. chim.*, 1931, **50**, 287; 1935, **54**, 275). No di-2-piperidyl was found.

Sabatier and Maihle (*Compt. rend.*, 1907, **144**, 784) investigated the vapour-phase hydrogenation of pyridine over nickel at temperatures ranging from 120° to 220°. No piperidine could be found in the product formed at 160—180° but a primary amine, believed to be *n*-amylamine (phenylurethane, m. p. 150°), was present in small amount. At 220° some *n*-pentane and ammonia were formed, a similar rupture of the nucleus having been observed earlier by Hofmann (*Ber.*, 1883, **16**, 590) on heating pyridine to 300° with hydriodic acid. Vapour-phase hydrogenation of pyridine to piperidine is now an established industrial process and recently (B.P. Appl. 7488/1948) Milner claimed that small amounts of high-boiling by-products are formed when nickel is used as catalyst. Dehydrogenation to pyridine was observed by Sabatier and Maihle (*loc. cit.*) when piperidine vapour alone was passed over nickel at 250°. Padoa and Carughi (*Atti R. Accad. Lincei*, 1906, **15**, 113) found that quinoline is transformed into methylindole by the action of finely divided nickel in the presence of hydrogen. Later Padoa (*ibid.*, 1907, **16**, 819), in rather inconclusive attempts to convert pyridine analogously into a pyrrolidine derivative, obtained indications of the formation of pyrrole derivatives. From piperidine and finely divided nickel under various conditions he obtained a mixture including pyridine, products of a pyrrole-like character, and two complex bases $C_{10}H_{21}N$ and $C_{14}H_{24}N_2$. In addition, he claimed that some ammonia was formed together with a mixture of combustible gases of a low carbon content, " probably hydrogen and methane."

In a more recent paper Saadikow and Michailow (*Ber.*, 1928, **61**, 421) described by-products of " an alkaloid-like nature " formed in appreciable amounts during the pressure hydrogenation of pyridine with osmium and osmium–cerium catalysts. Two main fractions boiling at 195—200° and 295—300°, giving crystalline derivatives, were probably $C_9H_{19}N$ and $C_{13}H_{20}N_2$ (approximating in composition to the bases described by Padoa), but the authors merely speculated about their identity.

These observations seem to indicate that during the catalytic hydrogenation of pyridine the piperidine which is first formed suffers hydrogenolysis in amount depending upon the conditions,

* Cf. Part I, *J. Soc. Chem. Ind.*, 1946, **65**, 169; Part II, *ibid.*, in the press.

and that the hydrogenolysis products react further to yield high-boiling by-products. Cleavage of the carbon–nitrogen bonds in quinoline and *iso*quinoline during high-temperature hydrogenation has also been reported (Rapoport, *J. Appl. Chem., U.S.S.R.*, 1936, **9**, 1456; Eru *et al.*, *J. Gen. Chem. Russia*, 1936, **8**, 1563; Yamaguchi, *Bull. Chem. Soc. Japan*, 1934, **9**, 303).

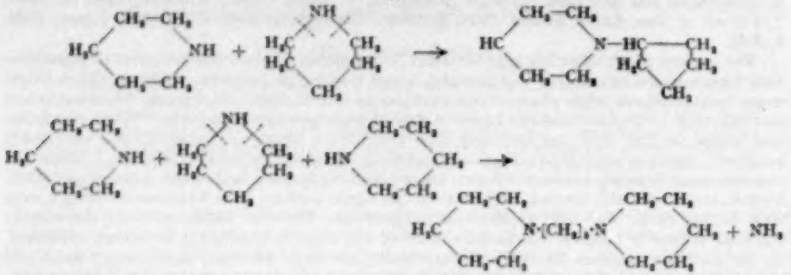
The present paper describes a preliminary investigation of the hydrogenolysis of piperidine with Raney nickel as catalyst. It has been found that in the presence of 10% of this catalyst some hydrogenolysis takes place at temperatures as low as 180°. Increasing the temperature and the time of contact leads to higher yields of hydrogenolysis products. When piperidine was heated at 230—250° for 12 hours with 10% of its weight of Raney nickel, only 9·3% survived; the total yield of liquid product, including unchanged piperidine, was 94%; ammonia, together with smaller amounts of the lower aliphatic amines and some gaseous paraffinic hydrocarbons, was also formed. Distillation the liquid product gave fractions covering a very wide boiling range, 80—300° at atmospheric pressure. Detailed examination of the various fractions is now in progress but already some of the major constituents have been identified. In the main the fractions consist of tertiary bases, but some secondary and primary bases and pyrrole derivatives are also present. The four major constituents are *N*-*n*-butyl-, *N*-*n*-amyl-, and *N*-*cyclo*pentyl-piperidine and 1 : 5-dipiperidinopentane. These have been isolated and characterised as picrates, hydrochlorides, and methiodides; for comparison the corresponding derivatives of the synthetic materials have been prepared. *N*-*n*-Butyl- and *N*-*n*-amyl-piperidine were synthesised from *n*-butyl and *n*-amyl bromide respectively. *N*-*cyclo*Pentylpiperidine was prepared from *cyclo*pentyl chloride and piperidine, and also by heating piperidine with *cyclo*pentanone in the presence of Raney nickel. Direct condensation of piperidine with pentamethylene dibromide or dichloride affords but little 1 : 5-dipiperidinopentane, the bulk of the product being the corresponding bispiperidinium halide (von Braun, *Ber.*, 1906, **39**, 4347; 1916, **49**, 972); however, as reported by von Braun, Kühn, and Goll (*Ber.*, 1926, **59**, 2330), treatment of this quaternary compound with excess of piperidine at a high temperature yields the ditertiary base. Alternatively, 1 : 5-dipiperidinopentane as the dihydrobromide may be obtained by hydrogenation of *NN'*-pentamethylenepyridinium dibromide in acetic acid with Adams's catalyst. Attempts to hydrogenate glutaroylpiperidine by the method of Adkins (*J. Amer. Chem. Soc.*, 1934, **56**, 2419; 1936, **58**, 2487), using copper chromite in dioxan, were not successful, the catalyst itself being reduced under the somewhat drastic conditions (250°/250 atmospheres) and the dioxan used as solvent showing signs of instability.

Some difficulty was experienced in separating and characterising the *N*-*n*-amylpiperidine owing to the co-existence of other bases in the same fraction. However, a clear-cut separation was achieved by selective elution from an ion-exchange column.

In the light of these observations and the measure of agreement between the melting points of some of the derivatives it seems likely that the $C_{15}H_{30}N_2$ base reported by Saadikow and Michailow (*loc. cit.*) was 1 : 5-dipiperidinopentane but in view of their somewhat obscure claims about the behaviour of certain derivatives it is doubtful whether the material they isolated was pure. Similarly, their $C_9H_{19}N$ base was probably *N*-*n*-butylpiperidine contaminated with some *N*-*n*-amyl- and possibly some *N*-*cyclo*pentyl-piperidine.

The formation of these tertiary bases from piperidine may be interpreted in terms of hydrogenolysis of piperidine with subsequent reaction of the primary products with unchanged piperidine. In the case of *N*-*n*-amylpiperidine, the carbon–nitrogen bond is cleaved with formation of *n*-amylamine, which with a mole of piperidine then gives ammonia and the *N*-*n*-amyl derivative (cf. Adkins and Winans, *J. Amer. Chem. Soc.*, 1932, **54**, 306). The formation of *N*-*n*-butylpiperidine is not so easy to explain but here again it seems likely that this has been formed by alkylation of piperidine with *n*-butylamine, another primary product of the reaction. In fact, *n*-butylamine has been identified in one experiment as a by-product of pyridine hydrogenation with Raney nickel, one carbon atom being eliminated. The missing carbon atom is accounted for by the presence of 2- and perhaps 3- and 4-methylpiperidine in the mixture. It is also interesting that *N*-methylpiperidine appears to be absent, which rules out cleavage resulting in methylamine. In one of the experiments starting with pyridine and hydrogen some α-picoline was detected; if the rupture of the piperidine nucleus occurs with formation of a methylene group, this could conceivably react with some of the unhydrogenated pyridine to give α-picoline. Likewise, when only piperidine is present, it reacts to give α-pipecoline. Both the pyridine and piperidine were distilled before the reactions and it is unlikely that either contained more than traces of their methyl homologues. Rupture of both carbon–nitrogen bonds in piperidine accounts for the formation of *N*-*cyclo*pentylpiperidine and

1 : 5-dipiperidinopentane; in both reactions ammonia is liberated by subsequent interaction with one and two moles respectively of uncleaved piperidine, thus:



It is evident from the complexity of the reaction product, which contains, in addition to the compounds mentioned, small amounts of secondary and primary bases, pyrrole derivatives, and gaseous hydrocarbons, that other modes of cleavage of the piperidine nucleus are also operative. The more detailed examination of the final products which is now in progress will, it is hoped, help to throw light on these other breakdown reactions.

Experimental.

(Microanalyses are by Drs. Weiler and Strauss and Miss M. Corner. M. p.s are uncorrected.)

Hydrogenation of Pyridine with Raney Nickel.—When redistilled pyridine, b. p. 115—115·2° (400 g.), was hydrogenated with Raney nickel * (20 g.) (Adkins and Covert, *J. Amer. Chem. Soc.*, 1932, **54**, 4116), at 200°/200 atmospheres for 12 hours in a 1-l. stainless-steel autoclave with stirring, the yield of piperidine obtained by distillation of the product was 83% (354 g.). Further distillation afforded unchanged pyridine (30 g.) and a residue (38 g., 9·0%), b. p. >125°.

When pyridine (400 g.) was heated at 300° in an autoclave with 5% of its weight of Raney nickel but without a hydrogen atmosphere 92% of the pyridine was recovered unchanged. High-boiling material, b. p. 160—180°/40 mm. (10 g.), yielded some di-2-pyridyl, m. p. and mixed m. p. 272°. Pyridine, therefore, apears to be remarkably stable under these conditions.

The liquid products from the four pyridine hydrogenation experiments were combined and were carefully fractionated in a 4-ft. Stedman column (1" internal diameter). At 150° the pressure was reduced to 20 mm. and distillation was continued again to 150° at which stage decomposition set in. Despite the use of vacuum there remained a fair amount of undistilled material. Although there were some obvious peak fractions among the distillates it did not seem worth while investigating them in detail. It is likely that the reactions taking place at 200° and at 330° are quite different. For this reason, and because of the failure to distil a significant portion of the mixed products little reliance could be placed on the interpretation of the results. However, in some of the fractions in the lower-boiling range of *n*-butylamine [picrate, m. p. 148° (Found: C, 39·5; H, 4·4; N, 18·4. Calc. for $C_{10}H_{14}O_7N_4$: C, 39·7; H, 4·6; N, 18·5%)] and α-picoline [picrate, m. p. 169° (Found: C, 44·5; H, 3·1; N, 17·3. Calc. for $C_{18}H_{10}O_7N_4$: C, 44·7; H, 3·1; N, 17·4%)] were identified. The fraction, b. p. 130—132°, gave a strong colour with Ehrlich's reagent and presumably contained pyrrole. A fraction, b. p. 142—143°, was suspected of containing β- and γ-picoline; the picrate obtained from it, although clearly not homogeneous, gave the correct analysis for methylpyridine picrate.

Treatment of Piperidine with Raney Nickel and Hydrogen at 250°.—Piperidine (1 kg., a close-cut fraction from distillation of commercial piperidine), with freshly prepared Raney nickel (100 g.) which had been washed with piperidine, was stirred in a 2-l. stainless-steel autoclave. Hydrogen was introduced to a pressure of 100 atms. before heating was commenced and the temperature was brought up to 250° and kept thereat for 12 hours. After cooling to room temperature the residual pressure in the autoclave was released, the issuing gases passing through scrubbers containing 1 : 1 hydrochloric acid solution to absorb ammonia or lower amines. The liquid contents of the autoclave were filtered, and the catalyst was washed with fresh piperidine (75 g.). The product was then heated under reflux to expel dissolved gases. An absorption train containing 1 : 1 hydrochloric acid solution removed ammonia or volatile amines; a sample of the scrubbed gas had the composition: CO_2, 0·7; C_nH_{2n}, 1·7; O_2, 10·8; CO, 0·2; H_2, 1·7; C_nH_{2n+2}, 38·0; N_2, 46·9. The value of *n* in C_nH_{2n+2} was 4·16. The total bases removed in the two scrubbing operations were determined, as ammonia, by making the acid solution up to a known volume, distilling the bases from an aliquot portion into *N*-hydrochloric acid, and back-titrating. Total bases gave a value of 67·2 g. as ammonia, and of this total 63 g. were ammonia itself (determined by the method of Wagner, Brown, and Peters, *J. Amer. Chem. Soc.*, 1947, **69**, 2612), the remainder presumably being lower amines.

The total yield of liquid product, including 75 g. of piperidine added to wash the catalyst, was 952 g.

* It is customary to store Raney nickel under alcohol. However, if ethyl alcohol is introduced with the catalyst for pyridine hydrogenation it reacts with the piperidine formed to give *N*-ethylpiperidine.

of which 12 g. was lost during the refluxing process. Total bases, as ammonia, made up only 1·7 g. of this loss, with ammonia itself contributing 0·8 g. It is thus clear from the gas analysis that dissolved hydrocarbon gases account for the major proportion. It is also likely that some of these neutral hydrocarbons were lost with the hydrogen on releasing the pressure in the autoclave. A preliminary distillation of the final liquid product yielded 365 g. of material boiling up to 147°. This fraction was fractionally distilled at atmospheric pressure in a 4′ × 1″ Stedman column (see Table I). The portion boiling above 147° (574 g.) was distilled at 5 mm. pressure in a Claisen flask with a 12″ indented side-arm, (see Table II); at 208° there remained only 28·8 g. of residue, which was beginning to decompose.

TABLE I.

Fractional distillation of low-boiling portion (365 *g.*).

Fraction.	Boiling range.	Yield, g.	Fraction.	Boiling range.	Yield, g.	Fraction.	Boiling range.	Yield, g.
1	<80°	11·4	13	102—104°	0·7	25	126—128°	4·8
2	80—82	0·3	14	104—106	3·0	26	128—130	2·9
3	82—84	3·3	15	106—108	93·0	27	130—132	3·0
4	84—86	3·3	16	108—110	5·0	28	132—134	1·7
5	86—88	3·6	17	110—112	2·6	29	134—136	0·25
6	88—90	8·2	18	112—114	3·2	30	136—138	0·8
7	90—92	1·3	19	114—116	2·7	31	138—140	0·25
8	92—94	2·0	20	116—118	3·2	32	140—142	0·6
9	94—96	0·75	21	118—120	5·6	33	142—144	1·0
10	96—98	0·9	22	120—122	4·0	34	144—146	1·8
11	98—100	0·8	23	122—124	2·3	35	146—148	0·6
12	100—102	0·9	24	124—126	3·9	Residue	—	44·0

TABLE II.

Fractional distillation (*at 5 mm.*) *of high-boiling constituents* (574 *g.*).

Fraction.	Boiling range.	Yield, g.	Fraction.	Boiling range.	Yield, g.	Fraction.	Boiling range.	Yield, g.
36	45—50°	45·0	43	84—100	13·6	50	135—150°	6·5
37	50—55	61·1	44	100—110	8·6	51	150—155	45·7
38	55—60	44·6	45	110—115	5·6	52	155—160	104·2
39	60—65	24·0	46	115—120	10·2	53	160—165	25·0
40	65—70	43·1	47	120—125	11·4	54	165—208	19·6
41	70—75	22·0	48	125—130	5·8	Residue	—	28·8
42	78—85	9·9	49	130—135	5·4			

Examination of the Liquid Products.—Fraction 15 consisted of almost pure piperidine; *N*-methylpiperidine, which has virtually the same b. p., could be detected by Hinsberg's method using benzenesulphonyl chloride.

Fraction 21 yielded from alcohol an orange-yellow picrate, m. p. 134°, but by repeated recrystallisation from acetone–light petroleum (b. p. 80—100°) (1 : 1) the m. p. was raised to 139° (Found: C, 43·85; H, 4·9; N, 17·3. Calc. for $C_{11}H_{14}O_7N_4$: C, 43·9; H, 4·9; N, 17·1%). A hydrochloride, m. p. 215° (Found: C, 53·05; H, 10·3; N, 10·3; Cl, 25·1. Calc. for $C_6H_{14}NCl$: C, 53·1; H, 10·4; N, 10·3; Cl, 26·1%), and a hydrobromide, m. p. 194—195° (Found: C, 40·2; H, 7·8; N, 7·9; Br, 44·0. Calc. for $C_6H_{14}NBr$: C, 40·0; H, 7·9; N, 7·8; Br, 44·3%), were obtained as colourless needles from acetone–alcohol. These analyses confirm the presence of a methyl homologue of piperidine; the b. p. agrees with that of (±)-α-pipecoline; recorded values of the m. p.s are: picrate, 134—135°; hydrochloride, 210°; hydrobromide, 189°. In view of the small yield of this base the possibility that it was present in the original piperidine cannot be ruled out, but this is considered unlikely. β- and γ-Pipecoline boil at 126—129°; although a small peak occurred in this distillation range, the fractions 24—26 were not homogeneous and gave no derivatives of constant m. p. Analyses of the derivatives, however, yielded values in agreement with those for a methylpiperidine. The slight reddish colour formed during attempts to prepare a hydrochloride from these fractions and the positive colour reaction with Ehrlich's reagent indicated the presence of some pyrrole. Fraction 27 gave a very marked colour with the reagent.

A very pronounced peak occurred at 80—55°/5 mm. This fraction (no. 37) consisted substantially (over 90%) of a tertiary base, but small amounts of primary and secondary bases were also present. The tertiary base, separated by treating a sample with benzenesulphonyl chloride, gave a picrate, m. p. 129·5° (Found: C, 48·9; H, 6·0; N, 14·9. Calc. for $C_{11}H_{16}O_7N_4$: C, 48·7; H, 6·0; N, 15·1%), hydrochloride, m. p. 232° (Found: C, 60·4; H, 11·2; N, 7·4; Cl, 19·6. Calc. for $C_6H_{14}NCl$: C, 60·8; H, 11·3; N, 7·9; Cl, 20·0%), and methiodide, m. p. 203° (Found: C, 42·5; H, 7·4; N, 5·0; I, 44·7. Calc. for $C_{28}H_{32}NI$: C, 42·4; H, 7·8; N, 4·95; I, 44·8%). The base regenerated from recrystallised picrate had b. p. 177° and n_D^{20} 1·4456 (Found: C, 76·8; H, 13·3; N, 10·1. Calc. for $C_9H_{19}N$: C, 76·6; H, 13·5; N, 9·9%) and yielded a hydrochloride and methiodide identical with those obtained as above. This base was identical with *N*-*n*-butylpiperidine (obtained from piperidine and *n*-butyl bromide), b. p. 176°, $n^{20\cdot3}$ 1·4446 (picrate, m. p. 130·5°; hydrochloride, m. p. 238·5°; methiodide, m. p. 206°). The small amount of secondary base present in the fraction was not identified, but when the mixed base fraction (1·5 g.) was treated with phenyl isocyanate (1·2 g.) a small amount of crystalline substance

(0·1 g.), m. p. 147° (Found: C, 72·8; H, 4·9; N, 12·5. Calc. for $C_{20}H_{17}O_3N_3$: C, 72·5; H, 5·1; N, 12·7%), was obtained.

By reaction with benzenesulphonyl chloride, fraction 40 was shown to consist principally of tertiary bases and their separation proved to be difficult. The only pure derivative prepared was a *methiodide*, m. p. 231° (decomp.) (Found: C, 44·6; H, 7·5; N, 4·4; I, 42·8. $C_{11}H_{22}NI$ requires C, 44·7; H, 7·5; N, 4·7; I, 43·0%). The same derivative, m. p. 230—231° (decomp.), was obtained in small amount from fraction 43, but here again its isolation proved somewhat difficult owing to the presence of another tertiary base. In the latter fraction secondary bases preponderated, but attempts to obtain crystalline derivatives therefrom were unsuccessful. The above methiodide corresponds to a base $C_{11}H_{21}N$ and, by synthesis, was shown to be *N-cyclo*pentylpiperidine. A *picrate*, m. p. 170° (Found: C, 49·9; H, 5·4; N, 15·0. $C_{17}H_{24}O_7N_4$ requires C, 50·5; H, 5·7; N, 14·6%), and a hydrochloride, m. p. 270° (Found: C, 63·3; H, 10·5; N, 7·6; Cl, 19·0. Calc. for $C_{11}H_{22}NCl$: C, 63·3; H, 10·65; N, 7·4; Cl, 18·7%), corresponding roughly to the same base, were obtained from fraction 43. Loevenich *et al.* (*Ber.*, 1929, **62**, *B*, 3084) give the analysis of this derivative but state no m. p.

*Synthesis of N-cyclo**Pentylpiperidine* (compare Loevenich *et al.*, *loc. cit.*).—Piperidine (8 g.) and *cyclo*pentyl chloride (4 g.) were refluxed for 8 hours and the mixture, after being made acid with hydrochloric acid, was extracted with ether. The bases liberated from the acid portion by addition of alkali were extracted with ether and, after being dried (NaOH), were distilled to give unchanged piperidine and *N-cyclo*pentylpiperidine (1·5 g.), b. p. 210° [methiodide, m. p. 230° (decomp.) (Found: C, 44·65; H, 7·4; N, 4·6; I, 43·0%)]. This derivative did not depress the m. p. of the methiodide obtained as above.

A 74% yield of *N-cyclo*pentylpiperidine, b. p. 210° [picrate, m. p. 174° (Found: C, 50·4; H, 5·8; N, 14·5%); hydrochloride, m. p. 277—278° (Found: C, 63·3; H, 10·5; N, 7·2; Cl, 18·9%)], was obtained by heating piperidine (45 g.) with *cyclo*pentanone (42 g.) and Raney nickel (10 g.) in an autoclave at 125—150° for 5 hours with an initial hydrogen pressure of 100 atms.

Separation of Bases in Fraction 40 (*b. p.* 65—70°/5 *mm.*) *by Ion-exchange.*—In addition to *N-cyclo*pentylpiperidine (see above) this fraction contained another tertiary base in considerable quantity but it was not possible to prepare pure derivatives for its characterisation. However, a fairly clear-cut separation was effected by means of an ion-exchange column consisting of a sulphonated, cross-linked polystyrene–divinylbenzene resin. The mixed base fraction (3 g.) was adsorbed on the column and *N*-hydrochloric acid in 50% ethyl alcohol was used to elute the bases. The effluent was collected every 40 ml. and by determining its conductivity at short intervals and on plotting of the results against the volume of effluent it was found that two constituents had been removed and that a useful separation had been accomplished. Further treatment of the column with 0·5*N*-potassium hydroxide in 50% ethyl alcohol removed a third component. The first series of effluent fractions, corresponding to the first minimum in the conductivity curve, yielded, after removal of the solvent under vacuum, the greater part of the original base mixture as a crystalline hydrochloride, m. p. 218° (Found: C, 62·4; H, 11·3; N, 7·9; Cl, 18·3. Calc. for $C_{11}H_{22}NCl$: C, 62·6; H, 11·5; N, 7·3; Cl, 18·5%), from which was also prepared a picrate, m. p. 109—110°. Neither of these derivatives on admixture with the corresponding derivatives of synthetic *N*-*n*-amylpiperidine (from *n*-amyl bromide and piperidine) caused any depression in the m. p. The other two constituents of the mixture removed from the column were not examined.

Examination of Fraction 52 (*b. p.* 155—160°/5 *mm.*).—This fraction was the most abundant; together with its immediate neighbours it represented 17·5% by weight of the original piperidine. Reaction with benzenesulphonyl chloride indicated that 94% of the bases in this fraction were tertiary. Further examination showed that at least 90% of the fraction could be accounted for as one base. Thus, when 30 g. of the fraction were treated with 65 g. of picric acid, 79·7 g. of an insoluble *dipicrate*, m. p. 197·5° (Found: C, 46·5; H, 5·2; N, 16·0. $C_{23}H_{30}O_{14}N_8$ requires C, 46·5; H, 5·2; N, 16·1%), were eventually obtained after a series of recrystallisations. From the picrate (10 g.) the free base (3·3 g.), b. p. 124—125°/1·5 mm., 142—144°/4·5 mm. (Found: C, 75·3; H, 12·6; N, 11·5. Calc. for $C_{11}H_{20}N_2$: C, 75·55; H, 12·7; N, 11·75%), was regenerated with dilute sodium hydroxide solution followed by steam-distillation. This base was di-tertiary and yielded a dihydrochloride, m. p. 259° (Adkins, *J. Amer. Chem. Soc.*, 1936, **58**, 2487; m. p. 253°), and a *dimethiodide*, m. p. 272° (decomp.) (Found: C, 39·1; H, 6·6; N, 5·0; I, 48·5. $C_{13}H_{32}N_2I_2$ requires C, 39·1; H, 6·9; N, 5·4; I, 48·6%). It was identified as 1 : 5-dipiperidinopentane.

Synthesis of 1 : 5-*Dipiperidinopentane* (cf. von Braun, *loc. cit.*).—Pentamethylene dichloride (10 g.), piperidine (15 g.), and water (10 g.) were heated on the steam-bath for 5½ hours. A further quantity of piperidine (5 g.) was added and heating continued for a further 4½ hours. The mixture was acidified with hydrochloric acid and extracted with ether to remove unchanged pentamethylene dichloride (4·1 g.). Addition of alkali, followed by steam-distillation removed excess of piperidine and any 1 : 5-dipiperidinopentane formed. These were extracted from the steam-distillate with ether, dried (NaOH), and distilled. A small fraction (1 g.) of 1 : 5-dipiperidinopentane remained after complete removal of the piperidine. This yielded a dipicrate, m. p. 197·5°, and a dimethiodide, m. p. 272° (decomp.), which gave no depression in m. p. in admixture with the derivatives described above. The involatile residue from the steam-distillation was made strongly alkaline with sodium hydroxide, whereupon a crystalline precipitate of the quaternary compound separated. As it was extremely hygroscopic it was necessary to remove water from this compound by azeotropic distillation with benzene. Dissolution in absolute alcohol followed by precipitation in sodium-dried ether yielded the quaternary compound (8 g.) free from sodium chloride. Dipiperidinium dichloride has no definite m. p.; decomposition sets in around 335°. Dipiperidinium picrate, m. p. 208°, crystallised from alcohol as long yellow needles.

Piperidine (213 g.), water (30 g.), and pentamethylene dibromide (115 g.) were heated in an autoclave with stirring for 5½ hours at 180—230°. After cooling, excess of 40% sodium hydroxide solution was added and the free bases were extracted with ether. The ethereal solution was dried (NaOH). From the total bases recovered (185·5 g.), excess of piperidine was distilled off leaving a residue of high-boiling base which yielded on distillation in a vacuum 1 : 5-dipiperidinopentane (81 g.), b. p. 124—125°/1·5 mm.

(Found : C, 75·3; H, 12·6; N, 11·5%) (dipicrate, m. p. 197·5° (Found : C, 46·5; H, 5·3; N, 13·3%); dimethiodide, m. p. 272° (Found : C, 38·9; H, 7·0; N, 5·25; I, 47·9%); *dihydrobromide*, m. p. 243·5° (Found : C, 45·1; H, 8·1; N, 6·3; Br, 40·0. $C_{11}H_{28}N_2Br_2$ requires C, 45·0; H, 8·0; N, 7·0; Br, 40·0%)).

Gautier and Renault (*Compt. rend.*, 1947, **225**, 682) have shown that *NN'*-polymethylene(bispyridinium halides) are obtained in good yield by heating pyridine with Hal·$(CH_2)_n$·Hal in ethyl alcohol. A nearly quantitative yield of pentane-1 : 5-(bispyridinium bromide) was obtained from pyridine and pentamethylene dibromide by this method. When the diquaternary compound (0·25 g.) was hydrogenated in acetic acid (10 g.) with Adams's catalyst (0·1 g.) at room temperature it took up the theoretical amount of hydrogen corresponding to reduction to 1 : 5-dipiperidinopentane dihydrobromide. The dihydrobromide (0·25 g.) was recovered as colourless crystalline needles, m. p. and mixed m. p. with the above dihydrobromide, 243° (Found : C, 45·1; H, 8·1; N, 6·3; Br, 40·0%).

This work formed part of the programme of the Chemistry Research Board and is published by permission of the Director of the Chemical Research Laboratory. I wish to acknowledge the valuable assistance of Mr. Sidney Hunt with the experimental work. Mr. D. K. Hale kindly performed the ion-exchange experiments and Messrs. E. C. Holt and A. Sleven carried out the distillation reported in Table I. The late Miss J. C. Connors collaborated in the early stages of the work.

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288. *The Nucleic Acids of Normal and Tumour Tissues. The Preparation and Composition of a Pentosenucleic Acid from the Fowl Sarcoma G.R.C.H.* 15.

By R. N. BEALE, R. J. C. HARRIS,* and E. M. F. ROE.

A pentosenucleic acid has been prepared from acetone-dried G.R.C.H. 15 fowl sarcoma tissue. The component pentose-nucleosides have been isolated and separated quantitatively by partition chromatography on a starch column. Adenine-, guanine-, cytosine-, and uracil-pentosides alone have been demonstrated and physicochemical evidence suggests that they are identical with those obtained from yeast ribosenucleic acid. The nucleic acid shows a wide divergence in composition from a "tetranucleotide" structure, and the molar ratio of purine- : pyrimidine-nucleosides is 4·83 : 3·23.

It is important that information should be gained about the structure of nucleic acids from different plant and animal sources. However, the analytical determination of components (*e.g.*, the ratio, purine : pyrimidine bases) gives limited information about the structure of a nucleic acid as it exists, in combination with proteins, in the cell (Brachet, *Growth Symposium*, 1947, **11**, 309; *Pubb. Staz. Zool. Napoli*, 1949, **21**, 77; Chantrenne, *Biochim. Biophys. Acta*, 1947, **1**, 437). Uncertainty arises because of the difficulty in assessing the extent of degradation which may occur during isolation.

Extraction of nucleic acid from tissues with alkali gives chemically degraded products. On the other hand, chemical procedures mild enough to be non-degradative *per se* provide optimum conditions for enzymic degradation. It might be expected, therefore, that pentosenucleic acids isolated after a more or less prolonged chemical treatment, even under the mildest conditions, consist of fragments of the "native" nucleic acid of varying molecular weights and degrees of enzymic degradation.

It is well known, for example, that the ribonuclease-resistant fraction of yeast pentosenucleic acid contains a higher proportion of purine bases than does the original acid. Moreover, there is, as yet, no evidence to justify an assumption that the nucleic acids derivable from different loci within the cell (*i.e.*, mitochondrial, microsomal, and nucleolar pentose-polynucleotides) are of identical structure. Pentosenucleic acids isolated by chemical methods and investigated from the point of view of the component bases, nucleosides, or nucleotides can therefore give little absolute information on the structure of "native" nucleic acids and the relationship of structure to possible specificity (both intracellular and inter-species). In the latter connection, the question of the specificity of the nucleic acids of malignant tissues needs to be examined. We propose to analyse the pentosenucleic acids of nucleoprotein–lipoprotein particles which may be isolated (morphologically intact) by physicochemical methods from filterable and non-filterable fowl tumours and from normal, non-malignant fowl and chick tissues. This, the first investigation, describes methods which may be used for the analysis of such pentosenucleic acids. The material investigated by us has been isolated by chemical extraction.

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The requirements for the analysis of most nucleic acids from the point of view of total composition are, first, that the methods used should be applicable to very small quantities, and, secondly, that the recoveries obtained should be quantitative.

Purine and pyrimidine bases have been separated by filter-paper partition chromatography (Vischer and Chargaff, *J. Biol. Chem.*, 1947, **168**, 781; *Fed. Proc.*, 1948, **7**, 197; *J. Biol. Chem.*, 1948, **176**, 703, 715; Chargaff, Vischer, Donniger, Green, and Misani, *ibid.*, 1949, **177**, 405; Vischer, Zamenhof, and Chargaff, *ibid.*, p. 429; Hotchkiss, *ibid.*, 1948, **175**, 315; *Colloques Int. Centre Nat. Recherche Sci.*, 1948, **8**, 57; Holiday and Johnson, *Nature*, 1949, **163**, 216; Markham and Smith, *ibid.*, p. 250; *Biochem. J.*, 1949, **45**, 298). Pentose nucleosides have also been separated under similar conditions (Hotchkiss, *J. Biol. Chem.*, 1948, **175**, 315), as have yeast pentose nucleotides (Vischer, Magasanik, and Chargaff, *Fed. Proc.*, 1949, **8**, 263; Carter and Cohn, *ibid.*, p. 190).

Ion-exchange resins have been used for the chromatographic separation of pentose-nucleosides (Harris and Thomas, *Nature*, 1948, **161**, 931; *J.*, 1948, 1936) and of purines, pyrimidines, and nucleotides (Cohn, *Science*, 1949, **109**, 377; *J. Amer. Chem. Soc.*, 1949, **71**, 2275; Carter and Cohn, *loc. cit.*; Smith and Wender, *J. Amer. Chem. Soc.*, 1948, **70**, 3719).

Hammarsten and his co-workers have preferred a partition column of starch similar to that employed for the separation of amino-acids by Stein and Moore (*J. Biol. Chem.*, 1948, **176**, 337), and separations of bases (Reichard, *ibid.*, 1949, **179**, 773; *Acta Chem. Scand.*, 1949, **3**, 422; Edman, Hammarsten, Löw, and Reichard, *J. Biol. Chem.*, 1949, **178**, 395) and of nucleosides (Reichard, *Nature*, 1948, **162**, 662; *J. Biol. Chem.*, 1949, **179**, 763) have been achieved. Daly and Mirsky (*ibid.*, p. 981) have also separated purine and pyrimidine bases by this method but, as in a considerable number of the other papers cited, have confined their attention solely to model systems comprising mixtures of pure components.

It is clearly an advantage to be able to separate and identify the largest possible fragments of a nucleic acid. Oligonucleotides are not yet characterised and the recent work of Cohn *et al.* (*loc. cit.*) has cast doubt on the structural characterisation of the pentose-nucleotides which have been prepared from yeast pentosenucleic acid.

The use of paper chromatography for the separation of purines and pyrimidines (the usual procedure) has several limitations. Vischer and Chargaff (*J. Biol. Chem.*, 1948, **176**, 703) claimed that optimum separations may be obtained with 20 μg. of the bases (with an estimated accuracy of recovery of ±6%). However, in the application of the procedures to other than model mixtures of pure components, difficulties were encountered in the quantitative hydrolysis of the nucleic acid, in the separation of the purines from the pyrimidines (an "upward correction" of 5% was applied to the pyrimidines recovered), in the tendency of cytosine to be deaminated to uracil during acid hydrolysis (see Loring and Ploeser, *ibid.*, 1949, **178**, 439), and in the evaluation of the "background correction" in the spectrophotometric determination of the bases, especially when the chromatogram had been run with solvents (such as pyridine and quinoline) which show a high ultra-violet absorption in the same region as the purine–pyrimidine bases. Moreover, as Markham and Smith (*Nature*, 1949, **166**, 1052) have again confirmed, there remains the possibility that purine bases themselves may decompose during acid hydrolysis.

It appeared, therefore, that milder methods of hydrolysis should be sought which would give large but still readily identifiable fragments of the nucleic acid and could be used to provide a complete analysis on a single sample of about 10—20 mg. (Chargaff *et al.* used 5—8 mg. for purine and 15—25 mg. for pyrimidine analysis).

In the light of the above arguments and for the reasons stated below, the method of analysis selected by us has been partition chromatography of nucleosides on starch columns. First, a supply of specimen yeast ribosenucleosides was available (Harris and Thomas, *loc. cit.*) for model separations and preliminary spectrophotometric examination; secondly, model experiments, described below, showed that mixtures containing as little as 1 mg. of each nucleoside could be separated and the individual nucleosides quantitatively recovered; and finally, mild, enzymic methods of hydrolysis of the nucleic acid were possible (Schmidt, Cubiles, and Thannhauser, *Cold Spring Harbor Symp. Quant. Biol.*, 1947, **12**, 161; Reichard, *J. Biol. Chem.*, 1949, **179**, 763).

*Preparation of a Pentosenucleic Acid from Fowl Sarcoma, G.R.C.H.*15.*—The nucleic acid was prepared from acetone-dried (delipidated) sarcoma tissue by a mild method, avoiding throughout a pH >7, and was purified through the barium salt by the method used by Jorpes (*Biochem. J.*, 1934, **28**, 2102) and by Davidson and Waymouth (*ibid.*, 1944, **38**, 375). The

* A non-filterable fowl sarcoma induced with 1 : 2-5 : 6-dibenzanthracene by Dr. P. R. Peacock (Glasgow Royal Cancer Hospital) in 1939, and since maintained by serial transplantation.

material thus obtained was a protein-free, pentose-containing nucleic acid giving no Dische reaction for deoxypentose (when the test was performed on small quantities). Alkaline hydrolysis by Schmidt and Thannhauser's method (*J. Biol. Chem.*, 1945, **161**, 83) showed that the product contained 94% of pentose-nucleic acid. The ultra-violet absorption spectrum is shown in Fig. 1. The infra-red absorption of this nucleic acid closely resembles that of a protein-free purified specimen of commercial yeast ribose-nucleic acid (Harris, Orr, and Roe, unpublished) and differs from that of a commercial sodium salt of calf-thymus deoxypentose-nucleic acid. Two preparations contained respectively: N (micro-Kjeldahl), 13·9, 13·8; P (microcolorimetric), 7·7, 8·2. The second preparation was used for hydrolysis.

FIG. 1.

Nucleic acid from G.R.C.H. 15 sarcoma.

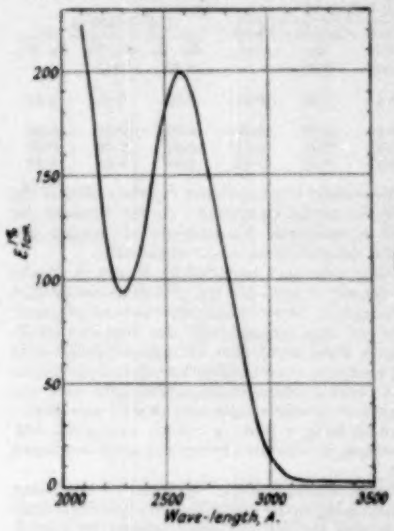
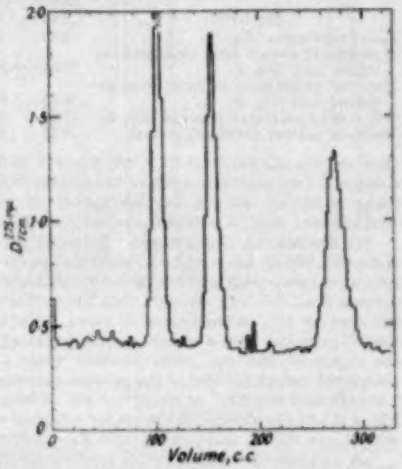


FIG. 2.

Model separation of pure nucleosides.



Separation and Identification of Nucleosides.—(a) *Model separation of pure nucleosides.* Fig. 2 shows the flow diagram for a mixture containing approximately 1 mg. each of adenosine, uridine, and guanosine. The starch column was prepared substantially by the method of Stein and Moore (*loc. cit.*). The nucleoside mixture was put on as a solution in a small amount of *n*-butanol saturated with water at room temperature (termed " saturated butanol " below). The chromatogram was developed with the same solvent and hourly fractions of eluate were collected continuously with the aid of a simple fraction-collecting machine (Cuckow, Harris, and Speed, *J. Soc. Chem. Ind.*, 1949, **68**, 208). Each fraction was examined in a 1-cm. absorption cell (distilled water as blank) in the Beckman DU spectrophotometer, and the optical density ($D = \log I_0/I$) at 275 mμ. was plotted against the volume of effluent. The fractions containing nucleosides were subsequently pooled, the solvent was removed as carefully as possible by evaporation *in vacuo*, and the nucleoside residue re-dissolved in 0·05*N*-hydrochloric acid for spectrophotometric identification and quantitative determination (for discussion of this, see below). The nucleosides were identified by means of their absorption spectra (aqueous solutions) and their relative and absolute R values (Table I) (Martin and Synge, *Biochem. J.*, 1941, **35**, 1358) where

$$R = \frac{\text{movement of position of max. concn. of solute}}{\text{simultaneous movement of surface of developing solvent in the empty column above the starch}}$$

The numerator in the above expression is equal to the length of the starch column in this

TABLE I.

Absolute and Relative R *values.*

Procedure.	Starch column (cm.).	Flow (c.c./hr.).	Volume (c.c.) at which band maximum occurred: adenosine.	uridine.	guanosine.	cytidine.
Model separation (Fig. 2).	20	2·5±0·2	103	153	272	—
Hydrolysate aliquot from yeast pentosenucleic acid (Fig. 4).	19	3·6±0·2	90	135	227	307
Pyridine hydrolysate of yeast pentosenucleic acid (Fig. 5).	19	3·2±0·2	91·5	153	303	380
G.R.C.H.15 pentosenucleic acid (Fig. 6).	20	3·2±0·2	98	147	225	299
Model separation (Reichard, *loc. cit.*).	—	—	—	—	—	—

	R (absolute).				*R* (relative).		
Procedure.	Adenosine.	Uridine.	Guanosine.	Cytidine.	$R_U : R_A$	$R_G : R_A$	$R_C : R_A$
Model separation (Fig. 2).	0·61	0·41	0·23	—	0·67	0·38	—
Hydrolysate aliquot from yeast pentosenucleic acid (Fig. 4).	0·68	0·44	0·26	0·20	0·66	0·39	0·30
Pyridine hydrolysate of yeast pentosenucleic acid (Fig. 5).	0·65	0·39	0·20	0·16	0·60	0·31	0·25
G.R.C.H.15 pentosenucleic acid (Fig. 6).	0·64	0·43	0·28	0·21	0·67	0·43	0·33
Model separation (Reichard, *loc. cit.*).	0·75	0·48	0·29	0·21	0·64	0·39	0·28

case and the denominator to $V/\pi r^2$, where V is the volume of effluent and r is the radius of the column. Two problems arose in connection with this model separation: (1) the necessity for using a solvent with a low absorption at the wave-length characteristic of purines and pyrimidines; and (2) evaluation of methods for the determination of the nucleosides.

(1) Purification of *n*-butanol. Normally purified *n*-butanol (supplied by Messrs. A. Boake Roberts and Co.) has a high and variable optical density at 260—270 mμ. Various purification procedures were tried in attempts to reduce this absorption, none of which was really satisfactory. Edman *et al.* (*loc. cit.*) reported that their solvent had been refluxed with zinc dust and alkali, followed by two redistillations *in vacuo*. We have since found that shaking *n*-butanol with freshly prepared Raney nickel catalyst produced a solvent of sufficiently low optical density in the region of 260 mμ. (with distilled water as blank). Since these experiments were not completed before the end of the present investigations, a wave-length was chosen such that a "background density" of about 0·4 was obtained on using a 1-cm. or 0·5-cm. absorption cell. Fig. 3 shows the absorption curves for a typical sample of *n*-butanol before and after treatment with Raney nickel, and storage over the catalyst.

(2) Evaluation of methods of spectrophotometric determination. In order to determine quantitatively the recovery of nucleosides after chromatographic separation two questions must be considered: (i) whether the appropriate fractions for one nucleoside should be pooled, evaporated to dryness, re-dissolved in a solvent, and determined by comparison with the absorption spectrum of the pure material in the same solvent; or whether the quantities found in each fraction of one chromatographic band (determined, as before, by comparison of optical densities with a standard absorption spectrum) should be summed, thus avoiding possible loss of material during evaporation; and (ii) by what means the contribution of "background absorption" due to solvent and/or starch may be evaluated.

Reichard (*loc. cit.*), who identified and determined individual nucleosides from evaporated, combined fractions, dissolved each residue in 10 c.c. of 0·1*N*-hydrochloric acid, and after dilution, measured the absorption between 240 and 310 mμ. The ratio $E_{max.}$: μg. of *N* per c.c. was determined for each nucleoside and compared with similar data for the standard compound. No correction was applied for "background absorption" caused by contamination with solvent or starch. This procedure appears to be sufficiently accurate for the comparatively large amounts (3·5—5·0 mg.) of nucleosides used in these model analyses, but it is possible that significant errors would be introduced in the analysis of smaller quantities owing to the increase in the proportion of "background absorption."

Daly and Mirsky (*loc. cit.*) separated purine and pyrimidine bases on columns of starch. Determination was carried out (*a*) by evaporation of combined fractions, dissolution in 0·1*N*-hydrochloric acid, and comparison of spectra with standards without correction for "background absorption," and (*b*) by summation of the weight of material corresponding to each fraction from one chromatographic band. They indicate that an average fraction before or behind the band should be used as a blank to correct for "background absorption."

Vischer and Chargaff used a different correction in experiments with paper chromatograms of bases. The difference between the optical densities at the relevant maximum and at 290 mμ. was taken as a basis for determination of the amounts of purine and pyrimidine present (dissolved out of a paper segment). This procedure is an attempt to eliminate a variable "background absorption" arising from contamination. It assumes, however, that this is constant in value from 290 mμ. throughout lower wave-lengths and, although a blank extract of paper was used in the comparison cell, this procedure is certainly not valid for our study of "background absorption" from starch columns.

Fig. 3.

n-Butanol.

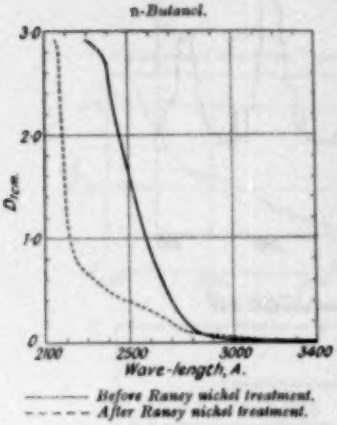
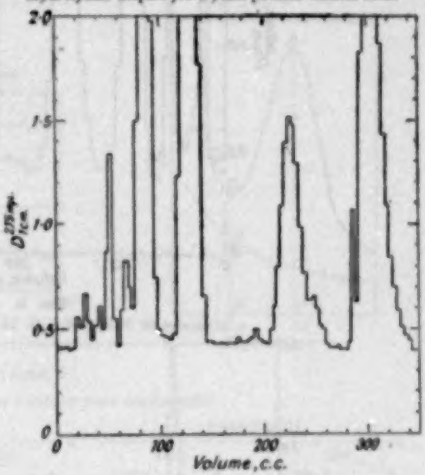


Fig. 4.

Hydrolysate aliquot from yeast pentose-nucleic acid.



In the following work, three methods have been used for determination of the nucleosides.

I. The combined fractions from one band were evaporated to dryness *in vacuo* and then dissolved in 5 or 10 c.c. of a suitable solvent (see below), and the maximum optical density, $D_{max.}$, of the solution was compared with that of a standard solution. No correction was applied for "background absorption."

II. In order to avoid possible losses during evaporation, calculations were made employing only the data from the flow diagram. From Figs. 4, 5, and 6 it may be seen that the "background absorption" before and behind a band is almost constant. For any particular fraction, therefore, the amount of nucleoside present may be calculated from the equation:

$$\text{Amount of nucleoside (mg.)} = MV(D - D_b)/\varepsilon l$$

where M = molecular weight of the nucleoside, D = observed optical density of the fraction, D_b = average of optical density of fractions before and behind the band, V = volume of fraction in c.c., l = cell length in cm., and ε = molecular extinction coefficient for the nucleoside.

These amounts may then be summed over the whole band. For the purposes of this calculation it is necessary to assume that the absorption spectrum of a nucleoside in saturated butanol is the same as that in water. This has been found to be true for adenosine, within 2% in the region of the maximum.

III. The combined fractions from one band were evaporated to dryness *in vacuo*, dissolved in 0·05*N*-hydrochloric acid, suitably diluted with the same solvent, and examined spectrophotometrically. "Background absorption" was determined from similarly treated effluent at the end of the chromatogram (fractions A–B, Fig. 6), and its spectrum is shown in Fig. 7. Interband fractions were also examined and found to contain very small amounts of nucleosides. These were also observed in minute amounts in fractions A–B. An interpolated correction

Fig. 5.

Pyridine hydrolysate of yeast pentosenucleic acid.

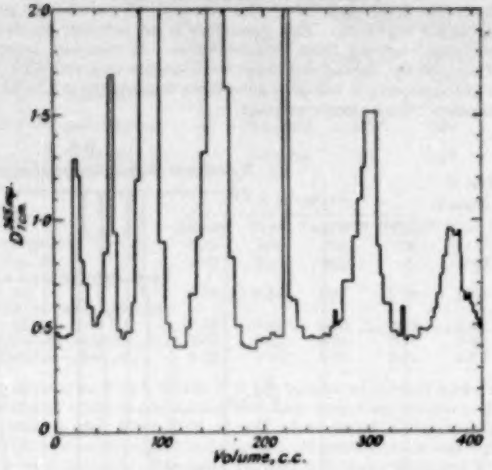
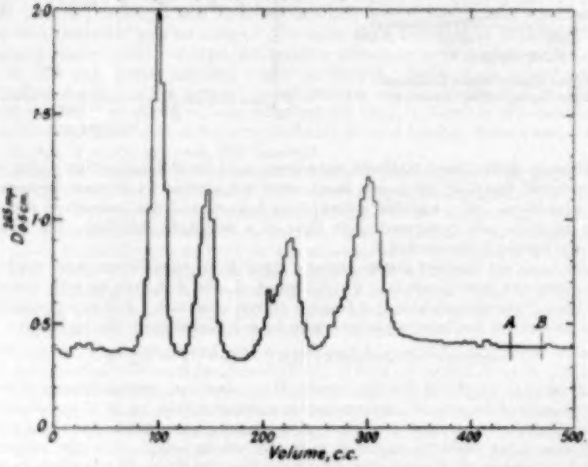


Fig. 6.

Hydrolysate from G.R.C.H. 15 pentosenucleic acid.



curve was therefore employed (cf. Fig. 7). This correction curve was used to eliminate "background absorption" in the following way :

Let ϵ_1 = extinction coefficient of recovered material at λ_1 (measured as $E^{s}_{1\,cm.}$, s being mg. per 100 c.c.),

ϵ_2 = do. at λ_2,

E_1 = extinction coefficient of pure material at λ_1 (measured as $E^{s}_{1\,cm.}$, s being as above),

E_2 = do. at λ_2,

ρ = ratio of "background absorption" from correction curve at λ_1 and λ_2.

From Fig. 8, e_1 = AC; e_2 = DF;
E_1 = AB; E_2 = DE;

Now BC/EF = (AC − AB)/(DF − DE) = $(e_1 - xE_1)/(e_2 - xE_2) = \rho$.

Thus $x = (e_1 - \rho e_2)/(E_1 - \rho E_2)$ mg.

In the application of this equation, any two wave-lengths may be used but it is preferable to work near the maximum and minimum of the nucleoside curve, so that $E_1 \gg E_2$.

In the model separations of pure nucleosides, methods I and III were used for the determination of recovery. The results are given in Table III. Table II shows the standard data employed, which were obtained from purified nucleosides (Harris and Thomas, *loc. cit.*).

FIG. 7.

"Background absorption" spectrum.

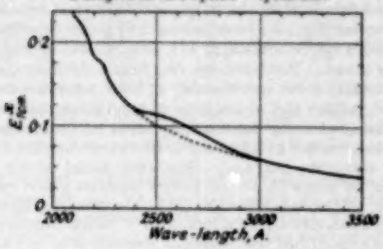


FIG. 8.

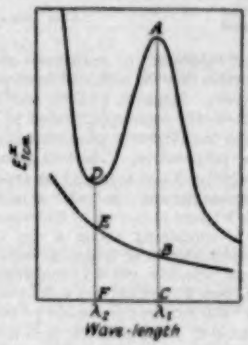


TABLE II.

Spectrophotometric data for pure nucleosides.

	0·05N-HCl.				0·05N-NaOH.			
	Max.,		Min.,		Max.,		Min.,	
	λ (mμ.).	ε.	λ (mμ.).	ε.	λ (mμ.).	ε.	λ (mμ.).	ε.
Adenosine ...	257	14,240	230	3360	259·5—260	14,550	229	2965
Guanosine ...	256	12,870	227·5	2720	266	11,480	231—231·5	4370
Uridine	262	10,170	230—230·5	2110	262	7,330	242	5300
Cytidine	279·5	13,210	240·5	1850	271·5	9,040	250	6300

In this table ε is the molar extinction coefficient given by

$\varepsilon = D/cl$, where $D = \log I_0/I$, c = concn. in g.-mol./l., and l = cell-length in cm.

TABLE III.

Comparison of recoveries of nucleosides in model experiments.

Recovery by :	method I (mg.).	method III (mg.).	Theor. (mg.).
Adenosine	1·20	1·12	1·05
Guanosine	0·99	0·85	1·03
Uridine	0·95	0·91	1·00

The recoveries from this model separation were considered to be satisfactory and the separation of nucleosides from hydrolysates of yeast ribosenucleic acid was next attempted.

(b) *Separation of the nucleosides derived from yeast riboss nucleic acid by hydrolysis with aqueous pyridine.* The nucleoside mixture was derived from an aliquot of an aqueous-pyridine hydrolysate (Bredereck, Martini, and Richter, *Ber.*, 1941, **74**, 694) of a very large quantity of commercial yeast nucleic acid. Guanosine had largely been removed by crystallisation and free phosphate by precipitation with barium hydroxide. Pyridine was absent. The chromatography was conducted in the usual way and the flow diagram is given in Fig. 4. No quantitative determinations were made, the nucleosides being merely identified by their absolute and relative R values (Table I). Qualitatively the separation was excellent, and a small quantity

(50 mg.) of purified commercial yeast nucleic acid was accordingly hydrolysed by this method and an aliquot (20 mg.) of the *total* hydrolysate prepared and chromatographed. The flow diagram obtained is illustrated in Fig. 5 and the corresponding R values in Table I. The four nucleosides were present as before, together however with other purine- and pyrimidine-containing substances such as adenine [$R = 1{\cdot}10$; Reichard (*loc. cit.*) gives $R = 1{\cdot}19$]. Spectrophotometric determination using method III showed that the recoveries were extremely small (Table IV).

TABLE IV.

Recoveries of nucleosides from aqueous-pyridine hydrolysate by method III.

	Mg.		Mg.
Adenine	0·08	Uridine	0·64
Adenosine	0·27	Cytidine	0·27
Guanosine	0·28		

(c) *Preparation of nucleosides from G.R.C.H.*15 *pentosenucleic acid by enzymic hydrolysis.* Nucleotides may be obtained from pentosenucleic acids in almost quantitative yield by alkaline hydrolysis. Schmidt, Cubiles, and Thannhauser (*loc. cit.*) have shown that nucleotides may be quantitatively dephosphorylated to nucleosides by incubation at 37° with an acid phosphatase obtained from hypertrophic human prostate gland. Reichard (*loc. cit.*) used a similarly derived enzyme preparation. The two groups of workers differ considerably in their estimates both of the stability of the enzyme in a crude gland extract and of the time of incubation required for dephosphorylation. Schmidt *et al.* recorded over 90% dephosphorylation of yeast adenylic acid in 3 hours (1 c.c. of 1 : 500 aqueous gland extract to 12 c.c. of 0·1N-sodium acetate buffer, pH 5·3, containing about 4 mg. of the substrate per c.c.). Reichard found about 85% dephosphorylation of a similar substrate in 20 hours (1 c.c. of 1 : 500 aqueous gland extract to 10 c.c. solution, pH 4·1, containing 1 mg. of the substrate per c.c.). In practice, Reichard used a fresh 1 : 100 extract and incubated the mixture for 24 hours at 37°. Model experiments with 1 : 100 extracts of human prostate gland confirmed the results of Schmidt *et al.* in that, at pH 4·5—5·0, yeast adenylic acid could be quantitatively hydrolysed to adenosine in 3 hours. To avoid the difficulty of obtaining fresh prostate tissue in view of the impossibility of storing an aqueous extract, the enzyme solution was prepared each time from an initial extract which had been dried from the frozen state.

Preliminary recovery experiments indicated that it was unwise to attempt to extract the nucleosides from the residue produced by the direct evaporation *in vacuo* of the nucleotide hydrolysate. Such a hydrolysate is acid and hydrolysis of purine nucleosides must occur on concentration. This may explain why Reichard obtained low overall yields of nucleosides from both adenylic and guanylic acids in his model experiments, and, in fact, adenine was obtained in the chromatogram.

It has been found that quantitative recoveries could be obtained if the pH of the hydrolysate was first raised to 7, the mixture was dried from the frozen state, and the nucleosides were extracted from the tractable residue with hot half-saturated butanol. Even under optimum conditions, however, guanosine is extremely difficult to extract and re-extraction of the residue with 0·05N-hydrochloric acid yielded a considerable quantity of guanosine.

Application of these hydrolytic procedures to the analysis of 11·7 mg. of the pentosenucleic acid from G.R.C.H.15, and chromatography of the nucleoside mixture under the standard conditions, gave the flow diagram shown in Fig. 6. Comparison of the R values with those obtained from mixtures of pure nucleosides, and from hydrolysates of yeast pentosenucleic acid, are given in Table I. Table V gives the quantitative determinations of the four nucleosides by the three spectrophotometric methods. It may be seen that methods II and III give results in close agreement, whereas method I gives higher values. Since no allowance is made in method I for "background absorption," this is to be expected. The absorption spectra of the various fractions in both 0·05N-hydrochloric acid and 0·05N-sodium hydroxide were compared with the standard data in Table II. The characteristic spectral shifts on change of pH (noted also by Hotchkiss, *loc. cit.*), together with the R values given in Table I, served to identify the four nucleosides.

The total recovery based on the nucleotide nitrogen of the nucleic acid was 85% (see Table VI).

The identity in behaviour, both chromatographically and spectrophotometrically, of the four nucleosides with the four nucleosides of yeast ribosenucleic acid renders it highly probable that these compounds are adenosine, guanosine, cytidine, and uridine.

TABLE V.

Comparison of recoveries (mg.) of nucleosides from G.R.C.H.15 by methods I, II, *and* III.

	Method I.		Method II.		Method III.	
Adenosine	—	0·92	—	0·89	—	0·83
Guanosine: fraction from chromatogram	0·93	—	0·73	—	0·81	—
extracted residue	2·18	—	2·13	—	2·13	—
total	—	3·11	—	2·86	—	2·94
Uridine	—	0·73	—	0·66	—	0·68
Cytidine	—	1·62	—	1·49	—	1·52
Total nucleoside recoveries	—	6·38	—	5·80	—	5·97

TABLE VI.

Analysis of G.R.C.H.15 pentose-nucleic acid.

Nucleoside calc. as	Mg. (method III).	% of sample.	% of hydrolysate (94% of sample).	N, % of hydrolysate-N.	P, % of hydrolysate-P.	Pur.-N / Pyr.-N	Molar ratio.
Adenosine ...	0·83	7·1	7·55	14·3	10·7	62·2	1·11
Guanosine*...	2·94	25·1	26·7	47·9	35·8		3·72
Uridine	0·68	5·8	6·2	5·15	9·6	22·45	1·0
Cytidine	1·52	13·0	13·80	17·3	21·5		2·23
Totals	5·97	—	—	84·65	77·6	2·8	—

* 0·81 Mg. of guanosine was recovered from the chromatogram, and the remainder by further extraction of the hydrolysate residue with 0·05*N*-hydrochloric acid. This solution had the spectrophotometric and chemical properties of guanosine.

Discussion.—At least 85% of the total nitrogen of the sample of tumour nucleic acid could be accounted for as the pentosides of adenine, guanine, cytosine, and uracil. The purine-*N* : pyrimidine-N ratio thus obtained (2·8) agrees with the value (2·8) found directly on a sample (of almost equal weight) by the method of Kerr and Blish (*J. Biol. Chem.*, 1940, **132**, 147), namely, hydrolysis of the nucleic acid with *N*-sulphuric acid and precipitation of the purines with copper hydroxide and sodium hydrogen sulphite. The composition of this nucleic acid, the first tumour nucleic acid to be examined in this way, differs from that of yeast ribosenucleic acid (deduced from paper chromatography of the bases by Chargaff *et al.*), from liver ribonucleic acid (Davidson and Waymouth, *loc. cit.*; evidence—purine : pyrimidine ratio)

TABLE VII.

	N, %.	P, %.	N : P.	Pur.-N / Pyr.-N	Adenine : Guanine : Cytosine : Uracil.
Yeast pentosenucleic acid	15·3	8·0	1·9	2·9	3·2 : 3·1 : 3·0 : 1·0
Pig-pancreas pentose-nucleic acid	15·4	7·9	1·95	4·0	3·6 : 6·8 : 4·5 : 1·0
Liver ribonucleic acid	15·0	6·7—7·6	2·1	1·4	— : — : — : —
G.R.C.H.15 pentose-nucleic acid	13·8	5·2	1·7	2·8	1·11 : 3·72 : 2·23 : 1·0

and from pig-pancreas pentose-nucleic acid (Chargaff *et al.*, *loc. cit.*—analysed by paper chromatography of the bases). These differences are tabulated in Table VII. The preponderance of guanosine in the tumour nucleic acid may be due to the fact that the material isolated is a nuclease-degraded fraction (as Chargaff has suggested for his pig-pancreas pentose-nucleic acid) but it may also be significant that the nucleic acid isolated by Claude (*Science*, 1939, **90**, 213) from a particulate cell fraction from another fowl sarcoma was stated to have an increased guanine content (see also Shemin, Sproul, and Jobling, *J. Exp. Med.*, 1940, **72**, 607). This is under investigation.

EXPERIMENTAL.

[With the assistance of J. F. THOMAS.]

Preparation of G.R.C.H.15 Pentosenucleic Acid.—Acetone-dried sarcoma tissue (30 g.) was mixed with 0·9% sodium chloride solution (1·5 l.) in a Waring blendor for 1—2 minutes and allowed to be extracted for 3 days at 0°. The suspension was centrifuged and the deposit re-extracted under the same conditions for 24 hours with a further 750 c.c. of sodium chloride solution. The combined supernatant liquids were treated with alcohol (4·6 l.), and the precipitate was collected by centrifugation. The deposit was dissolved in 0·9% aqueous sodium chloride (350 c.c.), the pH adjusted to 7·5 (glass electrode), and crystalline trypsin (25 mg.; containing 50% of magnesium sulphate) added. The flask was " layered "

with toluene and incubated at room temperature for 36 hours. The suspension was filtered (with the aid of "Hyflo Super-cel") and alcohol (2 volumes) added to the clear filtrate. The precipitate was collected as before, and dissolved in water (15 c.c.; final volume, 30 c.c.). The pH was adjusted to 7·2, and 20% barium acetate solution (30 c.c.; pH 6·8) added. The suspension was cooled to 0° and then centrifuged, the supernatant liquor rejected, and the deposit washed with 5% barium acetate solution (3 × 15 c.c.). The final deposit was extracted rapidly with ice-cold N-hydrochloric acid (10 c.c.), centrifuged, and washed with cold, distilled water (4 × 5 c.c.). The washed deposit was re-suspended in water (10 c.c.) and dissolved by the very cautious addition of 0·1N-sodium hydroxide to a final pH of 6·8. Care was taken to ensure that the solution never became alkaline. Glacial acetic acid was then added to bring the pH to 5·5. The solution was kept at 0° overnight, and a slight deposit centrifuged off. The pH was then brought to 1·0—2·0 with N-hydrochloric acid, and the nucleic acid precipitated immediately by the addition of alcohol (2 volumes). The colourless precipitate was collected by centrifugation and dried by being washed successively with 70%, 80%, 95%, and absolute alcohol and, finally, with dry ether. The product was then dried over phosphoric oxide *in vacuo*. Two preparations were made by this method. Preparation A (103 mg.) gave: N (micro-Kjeldahl), 13·0; P, 7·7%. Preparation B, (186·5 mg.), gave: N, 13·8; P, 8·2%. Both preparations were hygroscopic, gave strongly positive Bial reactions for pentose, and were qualitatively free from protein and deoxypentose (Dische reaction).

Deproteinisation by the Sevag procedure.—Preparation A (49·1 mg.) was dissolved in water (25 c.c.) by addition of 0·1N-sodium hydroxide to pH 7·0. The solution was shaken with successive 5-c.c. portions of 4 : 1 chloroform–amyl alcohol. The layers were separated by centrifugation. After several such treatments, 20·7 mg. of nucleic acid were recovered from the aqueous phase and had the same N : P ratio (1·6) as the starting material.

Preparation of Starch for Chromatography.—Commercial potato starch ("Farina," Corn Products Ltd., Strand, W.C.2) was freed from a yellow gummy contaminant by extraction with boiling methanol for 24 hours in a large Soxhlet extractor. The starch was then dried in a desiccator. The product was free-flowing and had a residual water content of about 10%, which must be taken into consideration in the preparation of the column.

Model Chromatogram with Pure Nucleosides.—Purified starch (40 g.) was made into a slurry with a mixture of n-butanol (70 c.c.) and water (12 c.c.). The slurry was poured into the conventional chromatographic column (25 cm. long × 2·0 cm. in diameter). The column was allowed to pack under gravity and was washed overnight with saturated n-butanol. The surplus head of solvent was then removed. Adenosine (1·05 mg.), guanosine (1·03 mg.), and uridine (1·0 mg.) were dissolved separately in the minimum quantity of cold, saturated n-butanol, mixed, and added to the column. Slight suction was applied and, when the solution had been almost completely absorbed, the column was washed again with the same solvent and the washing continued for 139 hours. Fractions were collected over hourly intervals with the aid of the automatic fraction collector. The rate of flow was 2·5 ± 0·2 c.c./hr. The recoveries are shown in Table III.

Chromatogram with an Aliquot of Aqueous-pyridine Hydrolysate.—The column was made from starch (40 g.) in the usual way. The nucleoside solution was derived from an aliquot of an aqueous-pyridine hydrolysate of a large quantity of yeast ribosenucleic acid by the procedure of Bredereck *et al.* (*loc. cit.*). Guanosine was largely removed by crystallisation and the free phosphate with barium hydroxide. The filtrate was freed from a slight excess of barium with sulphuric acid, and the precipitated barium sulphate was collected by centrifugation and washed once with hot water. The combined supernatant liquors were concentrated by evaporation *in vacuo* and finally dried in a vacuum-desiccator. 20 Mg. were dissolved in 3 c.c. of cold, saturated n-butanol and chromatographed in the usual way, 119 hourly fractions being collected. In view of the unknown quantitative constitution of the original hydrolysate, no attempt was made to estimate the nucleosides.

Chromatogram of Complete Aqueous-pyridine Hydrolysate.—Deproteinized (Sevag procedure) commercial yeast ribosenucleic acid (50 mg.) was refluxed for 108 hours with 50% aqueous pyridine (3 c.c.). The solution was then diluted with water to 10 c.c. and evaporated *in vacuo* to dryness. The residue was re-suspended in water (10 c.c.) and re-evaporated, and this process was repeated once more. The final residue was dissolved in water (30 c.c.), and saturated barium hydroxide solution was added to pH 9·0. The barium phosphate precipitate was removed by centrifugation and washed twice with cold water. N-Sulphuric acid was added to the combined supernatant liquor and washings to bring the pH to 7·4. The slight precipitate of barium sulphate was centrifuged off and the supernatant liquor evaporated to dryness *in vacuo*. The residue was then dissolved in saturated n-butanol (10 c.c.) and an aliquot (4 c.c., equivalent to 20 mg.) was then chromatographed in the usual way. Although qualitatively satisfactory, the separation was useless for quantitative analysis. (The recoveries are given in Table IV.)

Preparation of Crude Acid Phosphatase from Prostatic Tissue.—Hypertrophic human prostatic tissue (73 g.), which had been frozen in solid carbon dioxide within ½ hour of removal, was partly thawed, and disintegrated in a Waring blendor with water (250 c.c.). The cold mixture was filtered rapidly through surgical gauze to remove large fragments, and the filtrate rapidly dispensed in 10-c.c. aliquots into McCartney bottles and immediately dried from the frozen state in an Edwards Type 3 centrifugal freeze-drier. The dried contents of each bottle corresponded to 3 g. of wet tissue. The enzyme solution was prepared by shaking 50 mg. of the dry material with 10 c.c. of water until re-suspension had occurred. The mixture was then filtered with the aid of "Hyflo Super-cel," and the filtrate used immediately.

Model Experiments with Acid Phosphatase from Prostatic Tissue.—Samples of yeast adenylic acid were weighed into three tubes, A (23·3 mg.), B (25·5 mg.), and C (24·8 mg.). Each was suspended in 9 c.c. of water and brought to pH 5·0 (glass electrode) by the addition of 0·1N-sodium hydroxide (about 0·18 c.c.). The tubes were then equilibrated at 37° (thermostat). To A were added 2·8 c.c. of water and to B and C 1·8 c.c. of water and 1 c.c. of a filtered 1 : 100 extract of *fresh* human prostate. Aliquots of each were removed for determination of inorganic phosphorus after 5, 60, 120, and 180 minutes. The results are given in the table.

Time (mins.).	P liberated (mg.). A.	B.	C.	Time (mins.).	P liberated (mg.). A.	B.	C.
5	0·126	1·11	1·2	120	0·375	2·26	2·31
60	0·420	2·22	2·21	180	—	2·34	2·31

Extraction of Nucleosides from Enzymic Hydrolysates of Nucleotides.—Two mixtures of yeast ribonucleotides were prepared with the composition: (i) adenylic acid 5·7, guanylic acid 4·9, cytidylic acid 5·7, and disodium uridylate 5·4 mg.; and (ii) 5·3, 4·8, 6·3, and 5·6 mg., respectively. Each mixture was dissolved in 5 c.c. of 0·2*N*-sodium hydroxide, and the pH adjusted to 4·5 by addition of *N*-hydrochloric acid. 0·5 C.c. of filtered 1 : 100 extract of *fresh* prostate was added and the tubes were incubated at 37° for 3 hours. Aliquots were removed for determination of inorganic phosphate and indicated that 90 and 92·5% respectively of the total phosphorus had been split off. The contents of both tubes were then brought to pH 7 by addition of 0·2*N*-sodium hydroxide (about 0·15 c.c.). The residual content of each tube [(i) 8 c.c.; (ii) 9 c.c.] was halved and frozen-dried in McCartney bottles. One bottle of each was extracted with 2 × 5 c.c. of saturated *n*-butanol. Separation of an aqueous phase occurred and only 70% of the total nucleoside present was extracted (spectrophotometric determination of an equivalent mixture of the four nucleosides as standard). However, extraction of the material with 2 × 5 c.c. of warm aqueous *n*-butanol (half-saturated with water at room temperature) gave no phase separation and a 90% extraction.

Hydrolysis and Chromatography of the Pentosenucleic Acid of G.R.C.H.15.—24·25 Mg. of the pentosenucleic acid of G.R.C.H.15 were dissolved in 5 c.c. of 0·2*N*-sodium hydroxide and incubated at 37° for 18 hours. The pH was then adjusted to 5·0 with *N*-hydrochloric acid, 0·5 c.c. of prostate extract (from frozen-dried prostate) was added, and the incubation continued for a further 3 hours. The solution was then cooled to room temperature and brought to pH 6·9 with *N*-sodium hydroxide. The volume was adjusted to 15 c.c., and a 0·5 c.c. aliquot removed for determination of the liberated inorganic phosphate. 94% of the initial nucleic acid phosphorus was found in this fraction. The residual 14·5 c.c. were divided into two equal portions and frozen-dried. Each half thus contained 11·7 mg. of the original nucleic acid. The contents of one bottle were extracted with 2 × 5 c.c. of hot half-saturated *n*-butanol in the usual manner and the insoluble material was separated by centrifugation. The combined supernatant liquids were cooled to room temperature and carefully saturated by addition of water. This solution was then applied to a washed chromatographic column (40 g. of starch) and the chromatogram developed in the usual way. At the 13th hour the rate of flow was 3·5 c.c./hr. which decreased to 3·2 c.c./hr. at the 33rd hour and was maintained at this rate (±0·2 c.c.) for the duration of the separation (160 hours). The head of solvent over the column was 17·5 ± 1·5 cm. The flow diagram is illustrated in Fig. 6 and the recoveries are given in Table V. In view of the great insolubility of guanosine, the hydrolysate residue was re-extracted with 10 c.c. of 0·05*N*-hydrochloric acid and the resulting solution, containing pentose, gave ultra-violet absorption results characteristic of guanosine.

Estimation of Purine Bases in G.R.C.H.15 Pentosenucleic Acid.—The method used was a modification of that developed by Kerr *et al.* (*loc. cit.*) and is due to Dr. K. A. Smith of this Institute.

An aliquot, in a 15-c.c. centrifuge tube, of a solution of the nucleic acid at pH 7·0 containing 0·2—0·3 mg. of purine-nitrogen was adjusted to acid normality by addition of 4*N*-sulphuric acid and hydrolysed at 100° (water-bath) for 1 hour. The solution was then cooled to room temperature and neutralised (phenolphthalein) with 4% (w/v) sodium hydroxide solution, and 1 c.c. of 10% (w/v) cupric sulphate ($CuSO_4.5H_2O$) was added, together with more 4% sodium hydroxide solution until the suspension changed in colour from bluish-green to dark blue. The mixture was left for 30 minutes at room temperature and then centrifuged, the supernatant liquor being then decanted. The deposit was re-dissolved in 1 c.c. of 5% (v/v) sulphuric acid, and 4% sodium hydroxide solution was added until a small quantity of cupric hydroxide remained in suspension. This was re-dissolved by addition of one drop of glacial acetic acid. The tube was placed in a boiling water-bath and, when the contents had reached the bath temperature, 1 c.c. of 40% (w/v) sodium hydrogen sulphite solution was added and the suspension vigorously stirred. The tube was removed from the bath after 5 minutes and the stirring-rod and the sides of the tube were washed with 5% (w/v) sodium sulphate solution. The deposit was collected by centrifugation, the supernatant liquid discarded, and the deposit re-dissolved in 1 c.c. of 25% (v/v) hydrochloric acid. This solution (and any insoluble residue) was transferred to a micro-Kjeldahl digestion flask and digested in the usual way with sulphuric acid and hydrogen peroxide. This procedure was substantially that of Ma and Zuazaga (*Ind. Eng. Chem., Anal.*, 1942, **14**, 280) but no special digestion mixture was used and the ammonia was distilled in a Markham-type apparatus (*Biochem. J.*, 1942, **36**, 790). The total nitrogen content of a similar aliquot of the nucleic acid solution was determined by the same micro-Kjeldahl procedure. The determinations were performed in triplicate. 0·925 Mg. of purine-nitrogen was recovered from a total nitrogen content of 1·256 mg. The ratio of purine- : pyrimidine-nitrogen is thus 2·8 : 1. Model experiments with adenosine solution gave recoveries of purine nitrogen of 95—97% of the total.

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289. *Pickeringite and the System* $MgSO_4$–$Al_2(SO_4)_3$–H_2O.

By Henry Bassett and William Watt.

It has been shown that one double salt, $MgAl_2(SO_4)_4.22H_2O$, exists in the system $MgSO_4$–$Al_2(SO_4)_3$–H_2O at 25°. This is the essential constituent of pickeringite although all specimens of this mineral which we have examined contained excess of $MgSO_4.7H_2O$. Full analyses have been made of specimens of the mineral from widely differing localities and all disclosed a small excess of base which is probably caused by the presence of a small proportion of the soluble basic salt $Al_2O_3.2SO_3.11H_2O$. The general slight basic character of the conditions under which the mineral had been formed is further shown by the fact that all specimens contained, in intimate admixture, small amounts of insoluble alunite.

There is a group of minerals which are hydrated double sulphates of magnesium and aluminium, often containing appreciable amounts of zinc, manganese, or nickel. The molar proportions of magnesium and aluminium sulphates in these minerals range between about 1 : 1 and 6 : 1, and various names have been given to different members of the series (see Mellor, "Comprehensive Treatise of Inorganic Chemistry," **1924**, Vol. 5, p. 354; Hintze, "Handbuch der Mineralogie," **1930**, Vol. 1, section 3, ii, pp. 4503—4507). Pickeringite was first found at Iquique by Hayes (*Amer. J. Sci.*, **1848**, **47**, 360) who named it and gave it the correct formula. It has been gradually realised by mineralogists that probably only one definite compound, $MgSO_4.Al_2(SO_4)_3.22H_2O$, was involved, mixed with varying amounts of additional $MgSO_4.7H_2O$ (epsomite). This double salt is "pickeringite" but the whole series is often classed under this name. No real proof has hitherto been put forward of the correctness of the above view but this has now been provided by means of a phase-rule study of the system $MgSO_4$–$Al_2(SO_4)_3$–H_2O at 25°. The double salt has often been credited with $24H_2O$ and called "magnesia alum" from a false analogy with the true alums. The experimental results, when plotted in a triangular diagram, appear to decide definitely in favour of the $22H_2O$ formula in spite of the relatively unfavourable geometrical conditions.

Only the one double salt, $MgSO_4.Al_2(SO_4)_3.22H_2O$ [which should be written $MgAl_2(SO_4)_4.22H_2O$] exists at 25°. It is the stable solid phase in equilibrium with solutions covering the small range of concentrations (*a*) $MgSO_4$ 10%, $Al_2(SO_4)_3$ 21%, and (*b*) $MgSO_4$ 15·5%, $Al_2(SO_4)_3$ 16% by weight. As the double salt separates in fragile needle-like monoclinic prisms and as it does not form a congruent solution at 25° it is almost impossible to obtain it as a pure dry solid. It seems that specimens of pickeringite with almost the correct composition do occur sometimes but, as a rule, the mineral contains excess of magnesium sulphate.

Native $Al_2(SO_4)_3.16H_2O$, because of the more tabular habit of its crystals, occurs in a more massive form than the fibrous pickeringite with which it is not very likely to be confused. Intimate mixtures of the two compounds might be expected but do not appear to be frequent. The six specimens of pickeringite from different localities which we have analysed all contained excess of magnesium sulphate and *X*-ray photographs showed that this was present as the heptahydrate, epsomite. In the massive state the fibrous mineral seems to retain its water very well although the surface often has a slightly efflorescd appearance. Loss of water occurs more readily from the powdered mineral at ordinary temperatures in air of low humidity. One sample of the powdered mineral which had been kept for 6 months gave on analysis figures which corresponded to a mixture of the double salt with excess of $MgSO_4.6H_2O$ though the *X*-ray diagram taken before the grinding showed that the excess of magnesium sulphate was then present as heptahydrate. It is well known that $MgSO_4.7H_2O$ loses one molecule of water in a dry atmosphere at ordinary temperatures, so it is probable that excess of magnesium sulphate may be present in pickeringite as either hepta- or hexa-hydrate according to circumstances. Our specimens suggest that it is normally present as heptahydrate. All of them contained small or considerable proportions of one or more of the sulphates of Mn, Fe$^{\cdot\cdot}$, Co, Ni, Zn, K, and Na, and all appeared to be slightly basic. In several cases a small proportion of water-insoluble soda alunite was present.

Caven and Mitchell (*J.*, **1925**, **127**, 527) determined the 30° isotherm of the system $MnSO_4$–$Al_2(SO_4)_3$–H_2O and showed that one double salt, $MnSO_4.Al_2(SO_4)_3.22H_2O$, existed, known as a mineral called apjohnite. They found no double salt in the system $NiSO_4$–$Al_2(SO_4)_3$–H_2O at 30° (*ibid.*, p. 2549). Wirth (*Z. angew. Chem.*, **1913**, **26**, 81) gave the formula $FeSO_4.Al_2(SO_4)_3.24H_2O$ to the double salt which he found in the analogous $FeSO_4$ system, and which is identical with the mineral halotrichite, and Kane (*Trans. Irish Acad.*, **1837**, **17**, 423; *Phil. Mag.*, **1836**, [ii], **8**, 495; *Ann. Chim. Phys.*, **1839**, [ii], **72**, 368) considered the corresponding zinc salt to be $ZnSO_4.Al_2(SO_4)_3.24H_2O$ (recorded as a mineral under the very

unsuitable name zinc aluminite). There can be little doubt that both the ferrous and the zinc double salts are isomorphous with pickeringite and contain only $22H_2O$.

Experimental.

Suitable mixtures were prepared from distilled water and specially recrystallised and analysed $Al_2(SO_4)_3.16H_2O$ and $MgSO_4.7H_2O$. These were contained in glass tubes closed with waxed corks and rotated in a bath at 25° (thermostat) until equilibrium was reached, about 6 weeks being needed. The mixtures were filtered in a jacketed filter-tube, and the solution and the moist solid were analysed. Sulphate, alumina, and magnesia were determined. The solution was made 2N. with respect to ammonium chloride, a few drops of methyl-red were added, and then ammonia until the indicator just changed colour. The solution was then boiled for a few minutes, another drop or two of ammonia being added if necessary. The precipitated alumina was washed with 0·2N-ammonium nitrate till free from chloride, ignited to at least 1000° for an hour, and rapidly weighed.* One precipitation under these conditions gave a perfect separation from magnesium. Double precipitation of the magnesium as ammonium magnesium phosphate was necessary owing to the high concentration of ammonium salts. A single precipitation often gave high results, though not always.

The results obtained for the system $MgSO_4$–$Al_2(SO_4)_3$–H_2O are given in Table I and the figure; SO_3 found directly and the values calculated from the Al_2O_3 and MgO determinations are shown in Table I to give an idea of the correspondence achieved. The aluminium sulphate crystals obtained

Table I.

System $MgSO_4$–$Al_2(SO_4)_3$–H_2O *at 25°.*

Solution.						Moist solid.						
SO_3 found, wt.-%	SO_3 calc., wt.-%	$MgSO_4$, wt.-%	$MgSO_4$, mol.-%	$Al_2(SO_4)_3$, wt.-%	$Al_2(SO_4)_3$, mol.-%	$MgSO_4$, wt.-%	$MgSO_4$, mol.-%	$Al_2(SO_4)_3$, wt.-%	$Al_2(SO_4)_3$, mol.-%	SO_3 found, wt.-%	SO_3 calc., wt.-%	Solid phase.*
—	—	27·60	5·40	nil	nil	—	—	—	—	—	—	A
18·78	19·88	22·69	4·49	5·40	0·37	43·03	10·34	1·18	0·10	29·65	29·44	A
19·82	19·98	19·30	3·91	10·18	0·725	46·43	11·66	1·00	0·088	31·58	31·72	A
21·21	21·43	15·24	3·18	16·09	1·18	16·45	3·85	23·25	1·91	26·88	27·26	A, B
21·24	21·23	14·63	3·04	16·38	1·20	14·44	3·43	26·01	2·17	27·95	27·88	B
21·38	21·22	12·71	2·64	18·19	1·33	13·28	3·15	27·15	2·27	27·85	27·89	B
21·14	21·20	11·72	2·44	19·12	1·40	12·60	2·99	27·55	2·30	27·77	27·74	B
20·99	21·12	10·29	2·14	20·50	1·50	8·92	2·04	28·57	2·30	25·71	25·98	B, C
21·13	21·27	10·18	2·12	20·66	1·52	—	—	—	—	—	—	C†
20·71	20·97	8·39	1·74	21·92	1·60	6·62	1·47	28·19	2·20	23·92	24·18	C
19·99	20·17	3·45	0·71	25·48	1·84	2·32	0·536	34·87	2·63	25·77	26·02	C
—	—	nil	nil	28·20	2·03	—	—	—	—	—	—	C

Calc. for $MgAl_2(SO_4)_4.22H_2O$: $MgSO_4$ 14·01; $Al_2(SO_4)_3$ 39·84 wt.-% by wt. (both 4·17 mol.-%).
Calc. for $MgAl_2(SO_4)_4.24H_2O$: $MgSO_4$ 13·46; $Al_2(SO_4)_3$ 38·25 wt.-% (both 3·84 mol.-%).
* Solid phases: A, $MgSO_4.7H_2O$; B, $MgAl_2(SO_4)_4.22H_2O$; C, $Al_2(SO_4)_3.16H_2O$.
† Only phase C, but not analysed.

from the mixed sulphate solutions were like all other specimens of the normal hydrated salt. The tie lines show clearly that they consisted of $Al_2(SO_4)_3.16H_2O$ and thus confirm Bassett and Goodwin's conclusions (*J.*, 1949, 2244) as to the degree of hydration.

Analysis of Specimens of Pickeringite.—Several good clean specimens of this mineral were available and it was of interest to make full analyses of these and to consider the results in the light of the findings of the phase-rule investigation.

Specimens Nos. 1—4 consisted of white silky-looking masses of long, brittle, needle-like crystals. The Tucumcari mineral (No. 6) was in the form of separate large nodular aggregates of similar but shorter white needles which appeared to have formed in a sandy matrix. Specimen No. 5 was a white mass which looked as if it might have resulted from a thick paste of small crystals formed as a small pool dried up. It had not the fibrous nature of the other specimens.

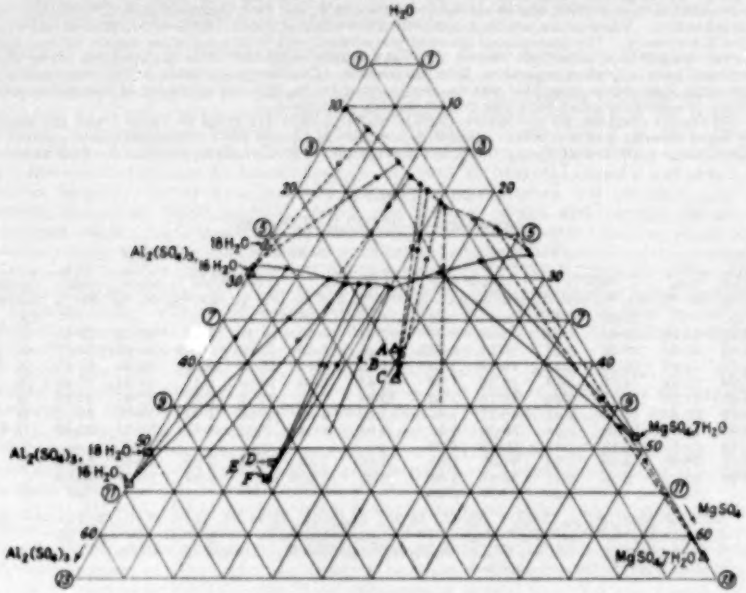
The material used for analysis was in each case selected so as to exclude any portion which was obviously not pickeringite. All the specimens were found to contain small proportions of some of the following: Na, K, Cu, Zn, Mn, Fe^{+3}, Co, and Ni; and it was important to determine these with reasonable accuracy, often with only limited amounts of the mineral. The following method was satisfactory.

* It is the authors' experience that alumina ignited under these conditions, though not quite non-hygroscopic, absorbs moisture slowly enough for perfectly satisfactory results to be obtained, probably with an error considerably smaller than the 0·4—0·8% of the amount present which is suggested by Hillebrand and Lundell ("Applied Inorganic Analysis," p. 386). Our practice was to allow the crucible to cool for 12 minutes in a desiccator containing activated alumina and then weigh on an air-damped balance with the weights already in position. The furnace temperature was often 1100° rather than 1000°. Though a temperature of 1200° will make the alumina quite non-hygroscopic it shortens very considerably the life of the expensive heating elements. This was the main reason for using the lower temperature.

The powdered mineral (2 g.) was treated with cold water and the solution filtered from any insoluble matter through a sintered-glass Gooch crucible. The insoluble matter was weighed after being washed with cold water and dried to constant weight at room temperature. It was kept for subsequent examination. The solution was made up to 100 c.c. 50 C.c. were used for the determination of aluminium, magnesium, and other metals, and separate 10-c.c. portions were used for that of sulphate, iron, manganese, and sodium.

In determinations of aluminium and sulphate the precautions mentioned by Bassett and Goodwin (*loc. cit.*, p. 2241) were taken.

25° *Isothermal of system* $MgSO_4$–$Al_2(SO_4)_3$–H_2O *plotted both in wt.-% and mol.-%.*



KEY TO FIGURE.

$A = 24H_2O$.	$D = 24H_2O$.
$B = MgAl_2(SO_4)_4$.	$E = MgAl_2(SO_4)_4$.
$C = 22H_2O$.	$F = 22H_2O$.

Full curves and tie lines and squares relate to wt.-%. Broken curves and tie lines, and triangles relate to mol.-%. The figures within circles at the sides of the diagram are mol.-%, the other figures are wt.-%.

Ferrous iron was determined by titration with 0·01N-permanganate. Total iron was then determined in the titrated solution colorimetrically with thiocyanate. It was found in all cases that the traces of iron in the water-soluble portions of the pickeringite were present entirely in the ferrous state.

Manganese was determined colorimetrically after conversion into permanganate by oxidation with persulphate in presence of silver nitrate. Addition of the latter showed whether any chloride was present. If so, the silver chloride could either be estimated nephelometrically, filtered off and weighed, or determined on a separate, larger amount of the mineral. If more than about 0·25% of manganous oxide is present in the mineral, only 1 c.c. of the solution should be used for the colorimetric determination.

Sodium was precipitated and weighed as sodium zinc uranyl acetate. Determination of aluminium, magnesium, etc., was carried out as follows: 5 G. of ammonium chloride were added to the 50-c.c. solution, which was then heated to boiling and saturated with hydrogen sulphide until cold. If an appreciable amount of zinc was present it was precipitated and next morning could be filtered off and washed with cold hydrogen sulphide water. It was ignited carefully, weighed as ZnO, dissolved in sulphuric acid, and precipitated as ammonium zinc phosphate which was weighed as $Zn_2P_2O_7$. (If only traces of zinc are present they are only precipitated with the analytical Group-IV metals, which may contain some even when larger amounts are present in the mineral.) Hydrogen sulphide was expelled from the zinc sulphide filtrate by boiling before precipitation of the alumina. Special analysis showed that when the amount of ammonium chloride stated was present a single precipitation of

aluminium with ammonia gave satisfactory separations from magnesium and the other metals present, and that double precipitation made no difference to the results. Separation from manganese was also proved to be complete in another way, as is shown later. It was found, however, that cobalt was always carried down in traces by the aluminium hydroxide and betrayed its presence by a slight blue colour of the ignited alumina. This was the case even when only very minute amounts of cobalt were present in the mineral.

Experiments were made in which known amounts of cobalt nitrate in very dilute solution were added to known weights of white alumina which, after being warmed to drive off the water, was ignited. These showed that the amounts of cobaltous oxide present in the alumina obtained in the pickeringite analyses were of the order of 0·0001—0·0005 g. and represented about 0·01—0·05% of the weight of alumina. This would correspond to 0·001—0·005% of cobaltous oxide in the original mineral. If the alumina obtained during the analysis was perfectly white it was evidence that the mineral being analysed contained much less cobalt than the amounts stated above. This carrying down of traces of cobalt by the alumina may be connected with the readiness with which cobalt is oxidised to the tervalent condition in alkaline solutions, but it may be that similar traces of all the other metals are also carried down but that their presence is not so easily detected. In any case the amounts would be too small to affect appreciably the general accuracy of the results.

2*N*-Ammonia (10 c.c.) was added to the filtrate from the aluminium hydroxide and the hot solution saturated with hydrogen sulphide. Next morning any precipitate was filtered off, washed with dilute colourless ammonium sulphide solution, and then extracted on the filter with hot 2*N*-hydrochloric acid which dissolved any manganous sulphide (and possibly a little zinc sulphide) and left any nickel and cobalt sulphide. The hydrochloric acid extract was evaporated to a very small volume, and the manganese precipitated as $NH_4MnPO_4.H_2O$ and weighed after ignition as pyrophosphate. For the further examination of the pyrophosphate see below.

The filtrate from the Group-IV sulphide precipitate was evaporated to drive off hydrogen sulphide and decompose polysulphides. The small precipitate of sulphur, with traces of nickel and cobalt sulphides, was filtered off and ignited along with these sulphides left on the filter paper after removing the manganous sulphide with 2*N*-hydrochloric acid. After being weighed, the mixed oxides were dissolved by heating them with a few drops of concentrated hydrochloric acid. The solution was evaporated to dryness, the chlorides were dissolved in a little water, and any nickel was precipitated with a suitable small amount of dimethyiglyoxime. The red nickel-dimethyiglyoxime was filtered off and weighed on a sintered-glass Gooch crucible, and the filtrate was evaporated to dryness in a porcelain crucible. The residue was ignited to drive off organic matter, and any cobalt oxide weighed, converted into sulphate, and again weighed. The presence of cobalt was confirmed by treatment with a very small amount of 1-nitroso-2-naphthol. The cobalt precipitate was ignited and weighed as Co_3O_4. The filtrate from any cobalt precipitate was evaporated to dryness and sometimes left after ignition a small residue of cupric oxide.

Magnesium was precipitated as $NH_4MgPO_4.xH_2O$ from the nickel–cobalt sulphide filtrate, filtered off, redissolved in hydrochloric acid, and reprecipitated as $NH_4MgPO_4.xH_2O$. After being weighed as pyrophosphate it was dissolved by warming it in the crucible with a few drops of 2*N*-sulphuric acid. Any flocks of carbon from the filter paper on which the $NH_4MgPO_4.xH_2O$ had been filtered off were removed and weighed. The filtrate was made up to 100 c.c., and 5 c.c. were used for a colorimetric estimation of any manganese present.

By deducting the corresponding weight of manganous pyrophosphate from the original "$Mg_2P_2O_7$" the true weight of the latter was obtained. The manganous pyrophosphate obtained from the solution of manganous sulphide in hydrochloric acid should also be dissolved in sulphuric acid and estimated colorimetrically, to confirm that it consisted entirely of manganous pyrophosphate and contained no zinc pyrophosphate, as was sometimes the case.

A proportion of the manganese was usually found in the magnesium precipitate. The sum of the manganese obtained as phosphate *via* manganous sulphide and that found in the magnesium precipitate was always equal to the total manganese determined colorimetrically in the original solution of the mineral. This is good evidence that single precipitation of the aluminium under the conditions stated gives a practically complete separation from manganese. As this has also been found to hold for magnesium it may be taken as applying fairly generally. The case of cobalt has been dealt with already.

Three specimens of pickeringite were available in sufficient quantity to allow determination of the trace of potassium present. The solution in water of 4 g. of the mineral, after being made 0·2*N*. with hydrochloric acid, was treated with a small excess of barium chloride. The filtrate from the barium sulphate was treated with 70% perchloric acid in excess of that equivalent to all the bases present. The solution was evaporated to the stage at which it just solidified on cooling. 20 C.c. of 97% alcohol were added to the crystallised mixture and after some time the trace of potassium perchlorate was filtered off on a sintered-glass Gooch crucible and weighed. It was then dissolved off the crucible (which was reweighed afterwards) with a little hot water, and the solution was concentrated and, after addition of a suitable amount of 5% chloroplatinic acid, evaporated to dryness at about 80°. The residue was treated with a small amount of 95% alcohol, and the minute amount of characteristic cubes and octahedra of potassium platinichloride filtered off and weighed on a sintered-glass Gooch crucible. The SO_3 required to form normal sulphates with the bases found was in all cases greater than the SO_3 found by analysis. The deficit of SO_3 ranged from 0·18 to 0·79% calculated on the mineral. The deficits are not large, but it is thought that they are genuine in view of the care taken with the analyses. Determinations of the excess of base in the water-soluble portion of the specimens were made by Craig's potassium fluoride method (*J. Soc. Chem. Ind.*, 1911, **30**, 184), using 2 g., or in one case (the Tucumcari specimen) 4 g., of the mineral. The proportion of free base shown was of the same order as that indicated by the sulphate determinations. Unfortunately, the end-point in Craig's method is somewhat indefinite so that the accuracy of the determinations is in doubt. The slight basicity is probably caused by a small amount of the water-soluble basic salt $Al_2O_3.2SO_3.11H_2O$ (Bassett and Goodwin, *loc. cit.*, p. 2246), which is of some interest since this compound has never been

found as a mineral and is not likely to occur as a separate relatively pure mineral because of its ready solubility and because it cannot form a congruent solution.

The basic sulphate is much more likely to be present as such than as a solid solution in the excess of $MgSO_4.7H_2O$ ($[AlOH(H_2O)_5]^{++}$ replacing $[Mg(H_2O)_6]^{++}$), since if the latter were the case it would imply the possible existence of $[AlOH(H_2O)_5]SO_4.H_2O = Al_2O_3.2SO_3.13H_2O$. We have seen no evidence for the occurrence of any hydrate of this basic salt other than $Al_2O_3.2SO_3.11H_2O$. $Al_2O_3.2SO_3.11H_2O$ is the only basic aluminium sulphate which dissolves rapidly in cold water and is thus the only one which could account for the behaviour observed with the pickeringites. It is slowly hydrolysed by pure water but can remain permanently stable in presence of solutions containing sufficient $Al_2(SO_4)_3$.

Our analyses of the pickeringite specimens are recorded in Table II. The case for a genuine small basicity of the water-soluble portion of the pickeringite specimens is greatly strengthened by the observation that, in several cases, the portion of the minerals insoluble in water consisted entirely or partly of soda alunite. At ordinary temperatures alunite always separates from solutions which are somewhat basic. In these pickeringites it occurs partly as a crystalline film between the crystal fibres of the pickeringite, but mainly as minute well-formed crystals, which shows that it does not represent fine alunite dust blown in from outside but that it had actually crystallised from the solutions which by evaporation had given rise to the pickeringite. Some separation of $Al_2O_3.2SO_3.11H_2O$ crystals during the drying up of such solutions is quite probable. It was considered necessary to show that this association of pickeringite with alunite is apparently quite general by making a full examination of the water-insoluble matter from as many specimens of pickeringite as were available. This was also desirable because of the interest attached to the deviations from the conventional alunite formula which are often shown by specimens formed at low temperatures, as those associated with pickeringite must have been.

The Alunitic Material Associated with Pickeringite.

(The numbers refer to the specimen numbers in Table II.)

1. The matter insoluble in water was very unevenly distributed and contained little alunite, as judged from its appearance. It was only weighed after ignition and consisted of dark and colourless isotropic glassy fragments.

2. The water-insoluble matter was extracted with hot concentrated hydrogen chloride, and the residue of angular quartz grains weighed. Only Al_2O_3 and SO_3 were determined in the acid extract. The amounts found would correspond to the presence in the mineral of 0·97% of an alunite of composition $Na[Al_3(OH)_6][SO_4]_2 + 0{\cdot}2\{Na[Al_3(OH)_8(H_2O)_4][SO_4]_2\}$.

3(*a*). The insoluble matter consisted of minute square rhombs and aggregates of these. They were strongly doubly-refracting and extinguished parallel to the diagonals of the rhombs. They had all the appearance of being crystals of alunite and gave an excellent *X*-ray diagram of that mineral. The loss on ignition (*i.e.*, $H_2O + SO_3$ not associated with Na_2O) was 53·1% and the Na_2O content 2·7%. This corresponds closely to the figures required by an alunitic mixture $Na[Al_3(OH)_6][SO_4]_2 + 1{\cdot}9\{H_2O[Al_3(OH)_6H_2O][SO_4]_2\}$.

3(*b*). The 4 g. of pickeringite used for the analysis contained 1·434% of air-dry water-insoluble matter though this was quite invisible in the mineral before treatment with water. It had a pale buff colour and consisted almost entirely of well-formed, though minute, doubly-refracting square rhombs of alunite. They were considerably larger than any obtained from other specimens of pickeringite. The distribution of the insoluble alunite in this specimen of pickeringite is somewhat erratic. Another 4 g. of the mineral adjacent to that used for the analysis and identical in appearance yielded only 0·208% of insoluble residue. As the pickeringite dissolved in the water it could be seen that some of the alunite was present in little pockets. Dissolution was allowed to proceed as quietly as possible and a little of the insoluble matter was taken out by means of a glass tube for microscopic examination. Some of the characteristic small rhombs could be seen, but also a considerable proportion of long thin flakes which showed uniform faint but quite distinct double refraction. Each flake polarized as a whole, suggesting that the flakes represented thin films of alunite intergrown with the pickeringite crystals and deposited from solution at the same time. The larger well-formed crystals seem to have been deposited in pockets among the crystals of pickeringite rather than on the actual faces of the growing crystals. Specimen No. 3(*b*) showed a number of brown inclusions just at places where groups of pickeringite prisms started off in different directions. It seemed likely that the brown material might consist of larger alunite crystals formed at about the same time as the pickeringite rather than just inclusions of clay or other foreign bodies. A quantity of the brownish material was accordingly separated and weighed 1·0541 g. It was washed with water to remove pickeringite, etc., and after being dried at 100° weighed 0·6220 g. (alunite does not lose water when heated at 100°). Microscopic examination showed it to consist mainly of undoubted small crystals of alunite with some particles which were probably quartz. It was hard to say whether any ferric oxide was present as such or whether much of the alunite was coloured. The 0·622 g. of alunitic material was digested with concentrated hydrochloric

TABLE II.

Pickeringite analyses.

Origin, etc., of specimens: (1) San Juan, Argentine (purchased as alunogen). (2) Iquique, Chile. (3*a*) South Africa (Imperial Institute 1735/26). (3*b*) South Africa, probably from Vioolsdrift, Namaqualand (Imp. Inst. 176344). (4) South America (labelled "Alumbre Sodico"). (5) South America (labelled "Alumbre Sodico"). (6) Tucumcari, New Mexico.

Number of specimen:	1	2	3*a*	3*b*	4	5	6
Insol. in acid, %	—	0·135	—	—	0·09	0·032	10·75
Sol. in acid but insol. in cold water, %	(1·69 after ignition)	0·97	0·81	1·434	0·04 after ignition	0·68	1·45
SO_3, %	35·60	36·93	36·00	34·58	36·10	35·42	32·42
Cl, %	0	0	0	0	trace	0·09	0
As $M^{III}Al_2(SO_4)_4.22H_2O$, %	9·40	10·62	5·78	5·97	5·44	8·23	8·53
Al_2O_3 (figure found), %	(10·03)	(10·97)	6·64	(6·53)	(9·13)	(9·25)	(8·74)
As $Al_2O_3.2SO_3.11H_2O$, %	0·63	0·35	0·86	0·66	0·69	1·02	0·21
MgO, %	5·45	5·06	10·08	9·76	7·19	6·66	5·55
MnO, %	Not determined (only trace)	0·05	0·23	0·23	0·23	0·18	0·76
FeO, %	"	0·007	<0·002	< 0·001	<0·001	0·17	0·01
CoO, %	0·002	trace	0·03	0·016	trace	—	absent
NiO, %	0·71	0·01	0·12	0·018	0·21	0·14	0·08
CuO, %	—	0·01	—	0·018	—	—	0·018
ZnO, %	0·94	—	0·01	—	0·37	0·76	absent
Na_2O, %	Not determined	0·08	0·476	0·042	0·03	0·036	0·034
K_2O, %	—	—	—	0·0056	—	0·0078	0·003
H_2O (by diff.), %	45·578	44·868	45·604	47·366	46·65	46·574	40·185
SO_3, calc. from bases as normal salts, %	36·092	37·204	36·68	35·10	36·64	36·22	32·60
SO_3, deficit by KF method, %	—	0·20	0·24	—	0·21	0·72	0·18
H_2O calc. for $M^{II}SO_4.7H_2O$, %	45·81	44·75	49·15	47·83	47·43	46·61	41·74
$M^{II}SO_4.6H_2O$, %	44·57	44·34	45·58	44·44	45·52	44·80	40·51
Approx. for $M^{II}Al_2(SO_4)_4.22H_2O$, %	78·3	89·4	48·7	49·4	71·0	69·3	71·6
$M^{II}SO_4.7H_2O$, %	15·9	5·6	48·9	46·2	26·2	23·7	16·3

Notes to Table II.—Nitrate was shown to be absent in Specimen No. 2, and absence of calcium was shown in Specimen No. 3(*b*). These ions were not looked for in the other specimens but were probably absent. The SO_3 percentage required to form normal salts with all the bases found was calculated for each specimen and was in all cases more than the amount actually found by analysis. On the assumption that the deficit was due to a portion of the alumina being present as $Al_2O_3.2SO_3.11H_2O$ instead of as pickeringite $MgAl_2(SO_4)_4.22H_2O$, distribution of the Al_2O_3 between these two salts was calculated and is shown in the table. The amount of MgO in the minerals was in all cases greater than that required to form pickeringite with the whole of the $Al_2(SO_4)_3$ present. It was assumed that the small amounts of other bivalent metals present were replacing magnesium isomorphously. The percentage of water which should be present in each specimen was then calculated on the assumption that the mineral was a mixture of $M^{III}Al_2(SO_4)_4.22H_2O$ and either $M^{II}SO_4.7H_2O$ or $M^{II}SO_4.6H_2O$. The sulphates of sodium and potassium were assumed to be present as such, in the anhydrous state. The values so calculated are shown in Table II. In four cases the water content found by difference in the analysis agrees very closely with that calculated for the presence of $M^{II}SO_4.7H_2O$. In two cases the experimental values agree with those calculated for the presence of $M^{II}SO_4.6H_2O$, and in one case the experimental result is about midway between the values calculated for hepta- and hexa-hydrate. The *X*-ray diagrams of Specimens 1, 3(*a*), 3(*b*), and 6 showed the same lines, but the diagrams of specimens 3(*a*) and 3(*b*) were different in that certain of the lines were relatively stronger. These lines were all present in the *X*-ray diagram of $MgSO_4.7H_2O$ as well as being present in the diagrams of all the pickeringite specimens. The approximate percentages of $M^{III}Al_2(SO_4)_4.22H_2O$ and $M^{II}SO_4.7H_2O$ present in each specimen calculated from the analyses are shown in Table II and explain the prominence of the $M^{II}SO_4.7H_2O$ lines in the *X*-ray diagrams of specimens 3(*a*) and 3(*b*). Owing to the complexity of the diagrams and the presence of the $M^{II}SO_4.7H_2O$ lines and probably of some due to $Al_2O_3.2SO_3.11H_2O$, it is uncertain what lines would be present in the *X*-ray diagram of a pure preparation of $MgAl_2(SO_4)_4.22H_2O$. The *X*-ray diagrams had been taken about five years before the full chemical analyses were made and show the presence of $M^{II}SO_4.7H_2O$ in all cases. Where the mineral had been kept in the massive state, little if any loss of water had occurred. The mineral 3(*a*) analysed was in small fragments of very thin fibres, while 3(*b*) was broken off a large lump. Specimen 6 had been ground and kept in a cardboard box for 6 months before analysis. The heptahydrate seems to have changed completely to the hexahydrate under these conditions. The presence of epsomite, $MgSO_4.7H_2O$, as an impurity in pickeringite has been recorded by Meixner and Pillewizer (*Zentr. Min. Geol.*, 1937, A, No. 9, 263). All the pickeringite specimens contained small amounts of material insoluble in water. Much of this, sometimes practically all, was soluble in acid and consisted of alunite. Methods for examining the small amounts of this material which were available were developed during the course of the investigation. Alunite is rhombohedral, crystallising in rhombs looking like cubes with angles of 90° 50′.

acid. The ferruginous matter quickly dissolved suggesting that it was $Fe_2O_3.H_2O$ rather than Fe_2O_3 or jarosite. As the iron went into solution the remaining mineral became practically colourless and on microscopic examination the square rhombs showed up well. Measured with a micrometer eyepiece, the largest crystals were found to have sides about 0·0125 mm. long. Complete dissolution of the crystals took a long time because of their relatively large size, but after 50 hours' digestion with acid, crystals of alunite could no longer be found among the portion still remaining undissolved, which seemed to be angular fragments of quartz. This was filtered off and washed; after air-drying it weighed 0·2276 g. and after ignition 0·2199 g. This small loss on ignition almost certainly means that a small proportion of alunite had still remained undissolved by the hydrochloric acid. The solution containing the 0·3944 g. of dissolved alunite was made up to 250 c.c. and analysed with the following results: Fe_2O_3, 23·46; Mn_2O_3, 0·21; Al_2O_3, 28·51; Na_2O, 4·67; K_2O, 1·55; SO_3, 29·64; H_2O (difference), 11·96%. These figures agree closely with those required by a mixture of $Fe_2O_3.H_2O$ 26·11% and $Mn_2O_3.H_2O$ 0·23%, with the alunite percentages, $Na[Al_3(OH)_6][SO_4]_2$ 60·22, $K[Al_3(OH)_6][SO_4]_2$ 13·63, and $H_3O[Al_3(OH)_6H_2O][SO_4]_2$ 0·42. Since this gives a total of 100·75% it is likely that some of the Fe_2O_3 is present as such.

4. The trace of insoluble matter in this specimen had only been weighed after ignition and not further examined. If its composition had been similar to that of the insoluble of Specimen No. 5 the percentage of air-dried insoluble matter would have been 0·09.

5. The portion of this specimen insoluble in water was flocculent and no crystals could be detected. Most of it dissolved fairly easily in hydrochloric acid. The material from 6·28 g. of the pickeringite was found to contain Na_2O 2·81, K_2O 1·67, Al_2O_3 35·30, Fe_2O_3 1·41, SO_3 31·97, and H_2O (difference) 26·84%. These figures agree exactly with those calculated for an alunitic complex which can be represented by the following mixture, given in wt.-%: $Na[Fe_3(OH)_6(H_2O)_2][SO_4]_2$, 3·81; $Na[Al_3(OH)_6(H_2O)_2][SO_4]_2$, 30·65; $K[Al_3(OH)_6(H_2O)_2][SO_4]_2$, 13·83; $H_3O[Al_3(OH)_6H_2O][SO_4]_2$, 22·81; $H_2O[Al_3(OH)_6(H_2O)_2]SO_4]_2$, 5·83; $H_3O(Al_3(OH)_4(H_2O)_2][Al(OH)_4]_2$, 23·07.

An interesting feature of this sample of alunitic material is that approximately 77% of the structure appears to have only two-thirds of the aluminium positions occupied.

6. The Tucumcari mineral contained a very variable and sometimes considerable amount of quartz sand in addition to alunite, the amount of which varied little and was of the order of 1·5%. The alunite was visible under the microscope as minute square crystals which were much smaller than those obtained from specimen 3(*b*) and so dissolved much more readily in acid. They contained Na_2O 4·32, K_2O 0·70, Al_2O_3 38·12, Fe_2O_3 1·43, SO_3 29·24, and H_2O (difference), 26·19%. The Fe_2O_3 may be present either as $Fe_2O_3.H_2O$ or as a constituent of the alunitic complex, and on either basis the figures correspond to a true alunitic complex. The figures are given for the case of the Fe_2O_3 being present as 1·59% of $Fe_2O_3.H_2O$. The remaining 98·41% of alunitic complex can be regarded as containing in wt.-%: $Na[Al_3(OH)_6][SO_4]_2$, 11·55; $Na[Al_3(OH)_6(H_2O)_2][SO_4]_2$, 41·30; $K[Al_3(OH)_6][SO_4]_2$, 6·15; $H_3O[Al_3(OH)_6H_2O][SO_4]_2$, 11·24; $H_3O[Al_3(OH)_4(H_2O)_2][Al(OH)_4]_2$, 28·16. It is to be noted that, while the alunite present in the South African pickeringite has the conventional formula, that in the American specimens has compositions much more like that of the synthetic alunites prepared by Bassett and Goodwin (*loc. cit.*, p. 2255). The calculated compositions of the alunitic complexes have been given in order to show that in spite of their variability all the analyses of the alunitic material were in fact consistent with a true alunitic composition.

It is, however, necessary to point out that the alunitic material from any one specimen of pickeringite is essentially a homogeneous isomorphous mixture. The types of replacement which are possible in the alunite structure are somewhat complex and, though such replacement occurs no doubt in a random manner, the method here used for showing the variation in composition of the alunites appears to be more convenient than that generally employed for indicating isomorphous replacement in silicate structures.

A number of *X*-ray spectrograms of pickeringite and other specimens were taken by Dr. T. H. Goodwin, Dr. G. H. Cheesman, and Dr. G. B. Greenough in connection with this investigation, and Dr. W. Cule Davies was instrumental in obtaining some of the pickeringite specimens. It is a pleasure to thank them for the valuable help thus given.

The phase-rule work described in this paper was done at Reading, the examination of the pickeringite mineral specimens at Widnes.

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290. *The Nucleic Acid Content of* Bact. lactis aerogenes.

By P. C. Caldwell and Sir Cyril Hinshelwood.

The deoxyribose nucleic acid content of individual cells of *Bact. lactis aerogenes* grown under a wide variety of conditions is found to be constant, as has been previously shown for certain nucleated cells. The ribose nucleic acid content and the cell size show marked variations.

The results suggest that the deoxyribose nucleic acid content is a major factor determining cell division in bacteria.

Measurements made with the filaments induced respectively by *m*-cresol and 2 : 8-diaminoacridine (proflavine) indicate that these substances disturb the cell morphology by different mechanisms.

The importance of the nucleic acids in cell processes is now generally conceded and has been accentuated by the recent observation (Boivin, Vendrely, and Vendrely, *Compt. rend.*, 1948, **226**, 1061; Mirsky and Ris, *Nature*, 1949, **163**, 666) that, for a given species of vertebrate, the nuclei of the somatic cells contain fixed amounts of deoxyribose nucleic acid.

For some time past, a systematic study has been made in this laboratory of the growth and metabolism of the coliform organism *Bacterium lactis aerogenes* and, as part of a wider investigation of the phosphorus metabolism, we have determined the ribose and deoxyribose nucleic acid content of cells grown under a wide range of conditions. As conditions vary, the ratio, bacterial mass : number of cells, which is a measure of the average size of the individual cells, shows considerable fluctuation. Consequently, one of our primary objects has been to find out whether, despite the alteration in cell size, the deoxyribose nucleic acid content of each cell shows anything like constancy. Information of this character should throw light on the function of nuclear material in bacteria. In particular, it might be relevant to the problem of adaptive changes, since, according to one hypothesis, cell division is attendant upon the attainment of a standard amount of certain key substances. The question arises whether these could be nucleic acids.

Cell Number and Cell Mass.—The number of cells in a culture was determined by counting in a hæmocytometer under the microscope. An estimate of the cell mass was obtained by measurement of the turbidity by means of a Spekker photoelectric absorptiometer. The turbidity has been shown by Monod ("La Croissance des Cultures Bactériennes," Paris, 1942) to be proportional to the dry weight of the cells contained in a given volume of culture. His conclusion is in general agreement with findings in this laboratory, that the turbidity is proportional to the organic-nitrogen content of the culture and that the ratio, turbidity : nitrogen content, is usually independent of the carbon source used by the cells. The absorptiometer readings are therefore converted into nitrogen contents by a calibration curve, and cell size has been expressed in terms of these quantities.

Estimation of Deoxyribose Nucleic Acid.—The deoxyribose nucleic acid was estimated by the Dische diphenylamine method (*Mikrochemie*, 1930, **8**, 4). In its original form this method is not entirely specific and certain modifications were therefore introduced. Fig. 1 *A* shows how the light absorption of thymus nucleic acid (measured by the scale reading on a Spekker absorptiometer) varies when the solution is heated with the reagent at 100°. A constant intensity is reached after 10 minutes.

Fig. 1 *B* shows the colour development in a washed suspension of bacteria subjected to an identical treatment, the cell debris being removed by centrifugation before the absorption is measured. Here a rapid initial rise in the colour intensity is followed by a phase of gradual development. The initial steep rise must be due to deoxyribose nucleic acid, and the subsequent slow development to other carbohydrate components. The deoxyribose nucleic acid content of the cells can be determined by extrapolation as shown, the intercept giving the intensity due to the nucleic acid itself. The amounts are expressed in terms of nucleic-acid-phosphorus by comparison with standard solutions of thymus nucleic acid.

Estimation of Ribose Nucleic Acid.—The ribose nucleic acid was estimated by a modification of the Bial pentose reaction (*Deutsche med. Woch.*, 1902, **28**, 253). The pentose in a solution was determined by treating 4 ml. of the solution with 4 ml. of 0·1% ferric chloride solution in 10*N*-hydrochloric acid and 2 ml. of 30% orcinol in absolute alcohol, 2-ml. samples of the resultant solution being heated in sealed tubes at 100°. Fig. 2 *A* shows the colour development, after various periods of heating, for a solution of yeast nucleic acid. (Blanks from samples containing no pentose have been subtracted from the values shown in the figure.) Maximum colour development occurs under these conditions after 25 minutes and a calibration curve can be constructed by heating standard samples of yeast nucleic acid with the reagents for 30 minutes. This calibration is expressed in terms of the phosphorus content of the nucleic acid.

Unfortunately estimations cannot be carried out directly on washed bacterial suspensions since the cells contain substances (probably proteins) which react with the reagent to give a brown colour. They can be largely eliminated by extraction of the nucleic acids with 7·5% trichloroacetic acid at 100° for 20 minutes. The colour development with a trichloroacetic acid extract is shown in Fig. 2 *B*. It is similar to that in the diphenylamine test. The initial rise is due to the purine ribonucleotides and the colour is a vivid green (pyrimidine ribonucleotides do not react with the reagent). The slow subsequent rise is due to interfering substances, and during this phase the samples become brownish-

yellow. The contribution to the colour made by the pentose is found by extrapolation to zero time (allowance being made for a 4-minute time-lag in the heating, indicated by the broken line in Fig. 2).

Estimation of Total Phosphorus.—Estimations of the total phosphorus were made to check the nucleic acid estimations. A given quantity of cell suspension was heated with sulphuric acid, potassium sulphate, and a trace of copper sulphate. After oxidation of all the organic material, the mixture was diluted to a known volume with distilled water and the pH adjusted to about 0. The orthophosphoric acid formed was estimated by a modification of the Berenblum–Chain method (*Biochem. J.*, 1938, **32**, 295). Since these estimations showed that 80—90% of cell-phosphorus could be accounted for as nucleic acid, the methods described in the preceding sections can be regarded as reliable.

General Procedure.—About 270 ml. of culture were grown to a standard bacterial count in a sterilised cylindrical vessel at 40°. 250 Ml. were centrifuged and washed 3 times with isotonic saline solution,

FIG. 1.

Colour development in Dische diphenylamine test: A, thymus nucleic acid; B, cell suspension.

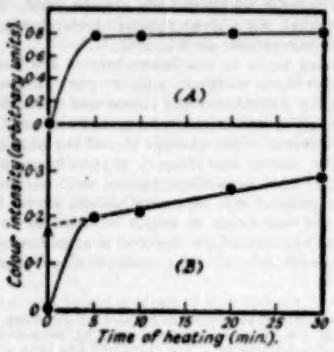
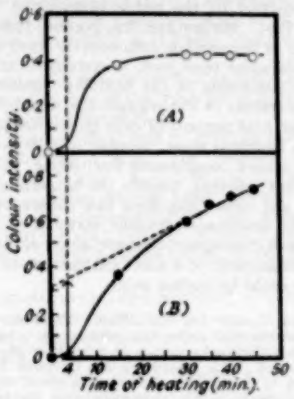


FIG. 2.

Colour development in the Bial pentose test: A, yeast nucleic acid; B, cell extract.



a pH measurement being carried out on the first batch of supernatant liquid. The cells were then made up to a final volume of 10 ml. with distilled water. 1 Ml. of cell suspension was diluted to 25 ml. for estimation of the cell count and the turbidity (the ratio, turbidity : hæmocytometer count, of the cells remained unaffected by the centrifugation). Further quantities of the suspension were then used for estimation of the deoxyribose, ribose, and total phosphorus.

Cultures Studied.—Cells were grown in a medium containing phosphate buffer, glucose, ammonium sulphate, and magnesium sulphate, aerobically and anaerobically. In some experiments veronal was added to the buffer and in others the glucose was replaced by malic or succinic acid as examples of alternative carbon sources. *m*-Cresol (0·8%), proflavine (2 : 8-diaminoacridine) (45 mg./l.), and colchicine (0·1%) were also added in some cases to the normal glucose medium, the first two because they are known, with this organism, to induce the formation of long filaments, the third because it is known to act in many cells as a mitotic poison.

DISCUSSION.

In Fig. 3 the deoxyribose nucleic acid content per cell is plotted against average cell size, expressed in terms of the amount of nitrogen per cell, for cultures grown under a variety of conditions. Fig. 4 shows a similar plot for the ribose nucleic acid content.

Fig. 3 shows that the deoxyribose nucleic acid content of *Bact. lactis aerogenes* is nearly constant despite pronounced variations in cell size. The values obtained represent an average, since the cultures examined contained cells at all stages of growth. Nevertheless, it appears that the deoxyribose nucleic acid constitutes a component which must be present in a fixed amount. It is not unreasonable, therefore, to suppose that the quantity present in an individual cell determines division.

On the other hand, the ribose nucleic acid content per cell shows marked variations (Fig. 4). Since the factors determining the actual amount of this acid are not yet clear, detailed discussion is postponed until further investigations have been completed. The present observations are, however, recorded to show the marked contrast between the two types of nucleic acid.

FIG. 3.

Deoxyribose nucleic acid content of cells grown under different conditions.

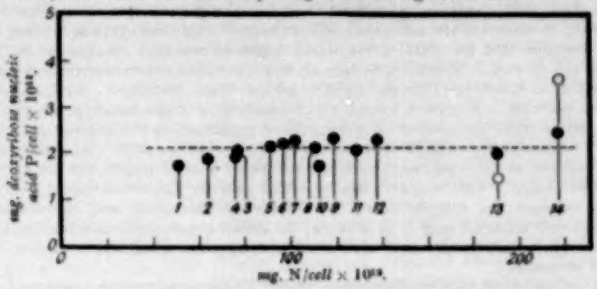
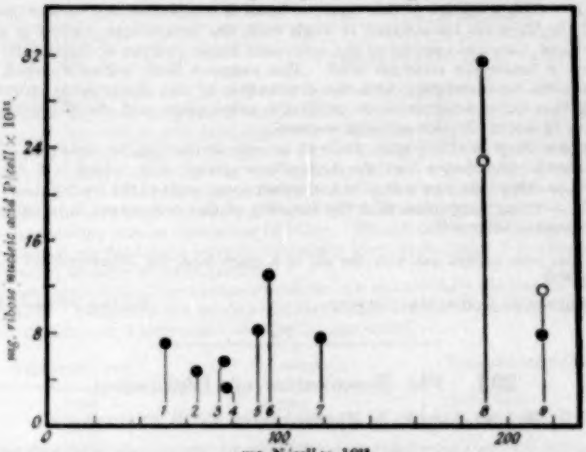


FIG. 4.

Ribose nucleic acid content of cells grown under different conditions.



KEY FOR FIGS. 3 AND 4.

Fig. 3	Fig. 4.		Final pH.
1.	1.	*Malic acid (aerobic ; logarithmic growth)*	7·7
2.	2.	*Succinic acid (aerobic ; logarithmic growth)*	7·8
3.	3.	*Glucose (aerobic ; logarithmic growth)*	6·1
4.	4.	*Mutant, induced by the irradiation of normal cells with ultra-violet light, in glucose, in which it grows very slowly (aerobic ; logarithmic growth)*	6·4
5.	5.	*Glucose (anaerobic ; stationary phase)*	4·7
6.	6.	*Glucose + 0·1% of colchicine (aerobic ; logarithmic growth)*	6·4
7.		*Glucose + veronal buffer ; phosphorus-deficient (aerobic ; stationary phase)*	4·4
8.		*Glucose (aerobic ; stationary phase)*	5·1
9.	7.	*Glucose + veronal buffer (aerobic ; logarithmic growth)*	5·7
10.		*Glucose + veronal buffer ; phosphorus-deficient (aerobic ; stationary phase)*	4·4
11.		*Glucose (anaerobic ; stationary phase)*	4·7
12.		*Glucose (anaerobic ; stationary phase)*	5·0
13.	8.	*Glucose + proflavine (45 mg./l.) (aerobic ; logarithmic growth). The shaded circle shows the deoxyribose nucleic acid per cell, each filament being regarded as a single cell. The open circle shows the content per cell, each filament being regarded as the equivalent number of cells of normal size*	5·4
14.	9.	*Glucose + 0·8% of m-cresol (aerobic ; logarithmic growth). The open circle shows the deoxyribose nucleic acid per cell, each filament being regarded as a single cell. The shaded circle shows the content per cell, each filament being regarded as the equivalent number of cells of normal size*	6·0

The effect of colchicine on the deoxyribose content will next be considered. Colchicine acts on nucleated cells as a mitotic poison, inducing polyploid forms. It has no obvious toxic effects on *Bact. lactis aerogenes* as judged from lag and growth rate, but, since this organism is now shown to resemble the nucleated cells in respect of its deoxyribose nucleic acid content, it seemed possible that an effect of colchicine might be revealed by changes in this quantity. In fact no such change is produced, though an increase in the ribose nucleic acid content occurs.

m-Cresol is a much less specific mitotic poison than colchicine. In 0·8% concentration in growing bacterial cultures it causes the formation of large numbers of long filamentous cells. If the deoxyribose content of these cells is expressed as the amount per cell, the value obtained is considerably higher than normal. If, however, each long filament is counted in the calculation as the equivalent number of cells of normal length, the deoxyribose content has the usual value. This suggests that *m*-cresol inhibits the cell-division process at a stage which lies between the completion of the deoxyribose structure and the actual fission. A *m*-cresol-induced filament might, in a sense, be called a polyploid bacterial cell. This character, however, is not permanent, and usually disappears when the cells are grown in the absence of *m*-cresol.

Proflavine also gives rises to filamentous cells. These appear when unadapted cells undergo their first sub-culture at a proflavine concentration just below that required for bacteriostasis. Large numbers of cells of about twice the normal size appear, together with a few filaments of greater length. With a culture of this type the result is complementary to that obtained with *m*-cresol. If the filaments are counted as single cells, the deoxyribose content is normal. If, on the other hand, they are counted as the equivalent larger number of single cells, the deoxyribose content is below the constant level. This suggests that, unlike *m*-cresol, proflavine produces filaments by interfering with the duplication of the deoxyribose structure. It is worth noting that rapid adaptation to proflavine takes place and the filaments disappear. No adaptation, however, is observed with *m*-cresol.

The work described in this paper, while in no way indicating the existence of a discrete nucleus in bacteria, has shown that the deoxyribose nucleic acid, which is a constant component of various other cells, can in fact be a constant component of the bacterial cell. Furthermore, there is a strong suggestion that the function of this component is in certain respects identical with that in other cells.

This work has been carried out with the aid of a grant from the Department of Scientific and Industrial Research.

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, February 8th*, 1950.]

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291. *The Bromination of Allylbenzene.*

By M. LORA-TAMAYO, F. MARTIN-PANIZO, and R. PEREZ OSSORIO.

The reaction between 1-phenylallyl alcohol and hydrogen bromide takes place with rearrangement, cinnamyl bromide being obtained instead of 1-phenylallyl bromide. In order to obtain the latter we have studied the reaction of *N*-bromosuccinimide with allylbenzene; the physical constants of the product and of its acetate are practically identical with those corresponding to the cinnamyl derivatives.

Ozonolysis of the carbinol obtained by the Grignard reaction of acetophenone with the bromo-derivative, and direct ozonolysis of the bromo-derivative, point to rearrangement in the action of *N*-bromosuccinimide on allylbenzene, cinnamyl bromide being obtained, with 1-phenylallyl bromide as an impurity. This result is confirmed by the infra-red spectrum of the bromide. The spectrum of the bromination product of diallyl showed that also in this case rearrangement accompanies bromination.

In the reaction of 1-phenylallyl alcohol with hydrogen bromide cinnamyl bromide

$$C_6H_5{\cdot}CH{:}CH{\cdot}CH_2Br$$

is obtained instead of 1-phenylallyl bromide $C_6H_5{\cdot}CHBr{\cdot}CH{:}CH_2$ (Moureu and Gallagher, *Bull. Soc. chim.*, 1921, [iv], **29**, 1009; Meisenheimer and Link, *Annalen*, 1930, **479**, 213; Lora-Tamayo and Perez Ossorio, *Anal. Fis. Quím.*, 1948, **44**, *B*, 981). Bouis (*Ann. Chim.*, 1928, **9**, 407), in experiments with various arylvinylcarbinols, established as a general rule that the transformation of secondary carbinols into bromo-derivatives is accompanied by rearrangement to give primary bromides. As we wished to prepare 1-phenylallyl bromide, we have studied the reaction of allylbenzene with *N*-bromosuccinimide, which Ziegler has proposed

(Ziegler, Späth, Schaaf, Schumann, and Winkelmann, *Annalen*, **1942**, **551**, 80) as a reagent for the bromine-substitution of allyl compounds in the α-position to the double bond.

Among the numerous recent applications of *N*-bromosuccinimide (Ruzicka *et al.*, *Helv. Chim. Acta*, **1943**, **25**, 1235; **1945**, **28**, 1360; **1946**, **29**, 473; Buu-Hoi, *Annalen*, **1944**, **556**, 1; Buu-Hoi and Lecocq, *Compt. rend.*, **1946**, **222**, 1441; *J.*, **1946**, 830; Lecocq, *Ann. Chim.*, **1948**, [xii], **3**, 62) including those which involve the use of catalysts (Karrer *et al.*, *Helv. Chim. Acta*, **1946**, **29**, 573), few cases are mentioned where bromination is accompanied by rearrangement. Karrer and Ringli (*Helv. Chim. Acta*, **1947**, **30**, 863, 1771) considered this possibility when they studied the bromination of diallyl, but concluded that the normal halogenation product, $CH_2{:}CH{\cdot}CH_2{\cdot}CHBr{\cdot}CH{:}CH_2$, is formed. Very recently, Braude and Waight, and Bateman, Cuneen, and Koch, in preliminary communications (*Nature*, **1949**, **164**, 241), have reported conclusions which agree with those now reached, *viz.*, that allylbenzene and diallyl undergo rearrangement on monobromination with *N*-bromosuccinimide.

We carried out the bromination according to the method of Ziegler and Lecocq and with a time of heating and molar relations similar to those adopted in the case of propenylbenzene. The brominated product, b. p. 132°/17 mm., resembled cinnamyl bromide. For its initial identification, we prepared the acetate by treating it with silver acetate in benzene and this had constants practically identical with those of cinnamyl acetate.

	B. p.	n_D^{20}.
Ester obtained	140—141°/10 mm.	1·5480
Cinnamyl acetate	139—140°/10 mm.	1·5464 *
1-Phenylallyl acetate	111°/10 mm.	1·5092 †

* Bouis, *Ann. Chim.*, **1928**, **9**, 407. † Dureen and Kenyon, *J.*, **1939**, 1697.

For the reaction product of diallyl with *N*-bromosuccinimide Karrer and Schneider (*Helv. Chim. Acta*, **1948**, **31**, 395) ascertained the structure by treating the bromo-derivative with magnesium and acetophenone and ozonizing the alcohol so produced. Using this method with our bromide from allylbenzene, we obtained a carbinol, m. p. 82°, which on ozonolysis yielded no formaldehyde, thereby showing that the bromide did not react as 1-phenylallyl bromide. Somewhat more direct evidence was obtained by ozonizing the bromo-compound directly. This gave benzoic acid in very small amounts (1·5% of the theoretical quantity), formaldehyde, and an unidentified reducing residue containing bromine. However, if the original product does not undergo rearrangement during the process, the results allow us to regard it as cinnamyl bromide, with 1-phenylallyl bromide as an impurity.

The infra-red spectrum of the bromo-derivative can undoubtedly disclose its structure with greater certainty. Thanks to the kindness of Mr. Henry Cohn of University College, London, we were able to obtain and interpret these spectra (see table).

Frequency, cm.$^{-1}$.	Intensity.	Probable assignment.
Bromo-derivative of allylbenzene.		
1598	strong	C=C bond
1202	very strong	C—Br bond
1077	strong	
965	very strong	$R_1{\cdot}CH{:}CH{\cdot}R_2$
747	very strong	monosubstitution
Bromo-derivative of diallyl.		
1203	very strong	C—Br bond
994	strong	$R{\cdot}CH{:}CH_2$
967	very strong	$R_1{\cdot}CH{:}CH{\cdot}R_2$
917	very strong	$R{\cdot}CH{:}CH_2$

Thompson (*Trans. Faraday Soc.*, **1945**, 249) showed that compounds of the types

$$R_1{\cdot}CH{:}CH{\cdot}R_2 \text{ and } R{\cdot}CH{:}CH_2$$

could be distinguished, inasmuch as the former give an intense band at 965 cm.$^{-1}$, and the latter bands at 909 and 990 cm.$^{-1}$. In our bromination product a very strong band occurs at 965 cm.$^{-1}$, which indicates the presence of the former grouping and weak bands at 998 and 985 cm.$^{-1}$, which can be attributed to a terminal double bond in very small quantity. The

other bands, entered in the table, correspond, as indicated, to the C–Br bond, to the mono-substitution, and also to the conjugation $C{:}C{\cdot}C_6H_5$.

The conclusion we reach is that the product examined is mostly, if not entirely,

$$C_6H_5{\cdot}CH{:}CH{\cdot}CH_2Br,$$

which confirms the occurrence of rearrangement in the bromination of allylbenzene with *N*-bromosuccinimide.

In view of this, the infra-red spectrum (see table) was obtained of the bromination product of diallyl, assumed by Karrer to be $CH_2{:}CH{\cdot}CHBr{\cdot}CH_2{\cdot}CH{:}CH_2$. The presence of strong bands at 994 and 917 cm.$^{-1}$ indicates the existence of the grouping $R{\cdot}CH{:}CH_2$, and the band at 967 cm.$^{-1}$ points to the existence of $R_1{\cdot}CH{:}CH{\cdot}R_2$. The compound concerned may be

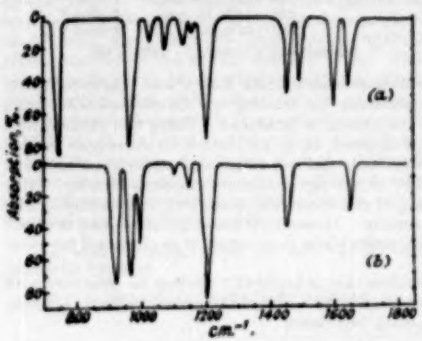
$$CH_2Br{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH{:}CH_2,$$

or a mixture of $CH_2Br{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH{:}CH_2$ and $CH_2{:}CH{\cdot}CHBr{\cdot}CH_2{\cdot}CH{:}CH_2$, or another. Whichever it is, the spectrum shows that in the bromination of diallyl partial rearrangement occurs. This does not agree with conclusions derived from chemical transformations.

Experimental.

Preparation of Allylbenzene.—Herzchberg's technique (*Helv. Chim. Acta*, 1934, **17**, 353) was followed but, instead of bromobenzene and allyl bromide, the corresponding iodine derivatives were used.

Reaction of Allylbenzene with N-Bromosuccinimide.—A solution of allylbenzene (22 g.) and *N*-bromosuccinimide (25 g.) in dry carbon tetrachloride (100 c.c.) was refluxed for 20 hours. The succinimide formed was separated, the solvent removed under reduced pressure, and the residue fractionated. After a small fraction of unchanged allylbenzene, the bromo-derivative, b. p. 118—120°/6 mm. (45—50%), passed over, and there remained a residue not yet investigated. The strongly coloured distillate was washed with a solution of sodium carbonate and redistilled in presence of anhydrous potassium carbonate. It then had b. p. 98°/1·5 mm. and, on addition of bromine, formed $C_6H_5{\cdot}CHBr{\cdot}CHBr{\cdot}CH_2Br$, m. p. 128°.



Transformation of the Bromo-derivative into the Acetoxy-derivative.—The bromo-derivative (7 g.), crystallized silver acetate (4 g.), and anhydrous benzene (60 c.c.) were refluxed for 2 hours, then another 2 g. of silver acetate were added, and another 2 g. after 10 hours. Boiling was continued for 30 hours. The silver bromide and the acetate residues were then separated, the benzene evaporated off, and the residue distilled under reduced pressure (b. p. 115/2·5 mm.; n_D^{20} 1·5480).

Condensation of the Bromo-derivative with Acetophenone.—To 1·1 g. of magnesium shavings, a solution of 9 g. of the bromo-derivative in 30 c.c. of anhydrous ether was added. When addition was complete, heating under reflux was carried out for 1—1·5 hours, followed by cooling in an ice-bath. 5 g. of acetophenone dissolved in 15 c.c. of anhydrous ether were then added dropwise. When the reaction was complete, heating was continued for another 2 hours, with stirring. The magnesium compounds were decomposed with aqueous ammonium chloride and the mixture extracted with ether; the ethereal solution was washed with water and dried (Na_2SO_4): the solvent was removed, and the residue was distilled *in vacuo*. The unchanged acetophenone fraction was separated and the residue allowed to crystallize in a freezing mixture. It was then collected and recrystallized from alcohol. A white *product* was obtained (small nacreous laminae), m. p. 82° (Found: C, 85·6; H, 7·7. $C_{17}H_{16}O$ requires C, 85·7; H, 7·6%).

Ozonolysis of the Carbinol.—In all experiments we employed an ozonizer which produces 5—7 mg. of ozone per hour at a speed of passage of 90—100 bubbles per minute. The temperature of the solution to be ozonized was −15°.

The carbinol (0·254 g.) in pure carbon tetrachloride was ozonized until no more ozone was absorbed. Water (50 c.c.) was added to the solution, which was then refluxed for 3 hours, the end of the condenser being connected by a glass tube to a vessel containing 20 c.c. of water (*A*) cooled in ice (Sorm and Urbanek, *Coll. Trav. chim. Tchécosl.*, 1948, **13**, 425). The aqueous layer and the water (*A*) were distilled, 0·2 g. of dimedon was added, and the whole boiled for 10 minutes and set aside for 24 hours. No crystallization was observed.

The solvent was evaporated from the carbon tetrachloride layer, the residue was dissolved in ether, extracted several times with a 15% sodium carbonate solution and washed with water, and the ether was evaporated off. The residue then gave a semicarbazone, m. p. 209° (from methanol). The m. p. of benzaldehyde semicarbazone is 210°; mixed m. p. was 209°.

Ozonolysis of the Original Bromo-derivative.—In the same way 0·3880 g. of the bromo-derivative was ozonized. The ozonide formed was decomposed by Batt and Slater's technique (*J.*, 1949, 838), and three solutions were obtained; (*A*) aqueous solution, (*B*) ethereal extract of neutral products, and (*C*) fraction soluble in aqueous sodium carbonate.

(*A*) treated as above, gave 0·0060 g of a product, m. p. 187° (from alcohol) (the formaldehyde-dimedon complex has 187°; mixed m. p., 187°).

(*C*) was acidified with hydrochloric acid and extracted with ether. When the solvent had evaporated, the residue, recrystallised from water, melted at 122°; it was benzoic acid.

(*B*) gave, after removal of the solvent, a thick yellow liquid which contained bromide and readily reduced Fehling's solution. This liquid decomposed on distillation *in vacuo*, and neither a semicarbazone nor a crystalline 2 : 4-dinitrophenylhydrazone could be obtained.

Infra-red Spectra.—A D209 Hilger spectrometer for infra-red was used. The compounds were studied as liquids, between rock-crystal plates of 0·005—0·1 mm. thick. The spectra comprised the range 5—15 μ, and the frequency accuracy was at least $\pm$ 2 cm.$^{-1}$. The figure shows the spectrograms of the bromo-derivatives of allylbenzene (*a*) and diallyl (*b*) obtained with *N*-bromosuccinimide.

Diallyl.—This was prepared, either by the action of the zinc–sodium alloy on allyl iodide, or according to Turk and Chanan (*Org. Synth.*, 1947, **27**, 7), allyl iodide being used instead of the chloride. Bromination was effected with *N*-bromosuccinimide, according to Karrer and Ringli (*loc. cit.*), the monobromo- (b. p. 40—45°/10 mm.) being fractionated from the dibromo-product (b. p. 115—120°/40 mm.).

Thanks are tendered to Prof. C. K. Ingold, F.R.S., for making available the facilities of his Spectroscopic Department.

INSTITUTE "ALONSO BARBA" OF CHEMISTRY OF THE C.S.I.C.
DEPARTMENT OF ORGANIC CHEMISTRY, MADRID.

[*Received, February 7th*, 1950.]

NOTES.

The Reduction of Uranium Hexafluoride with Hydrogen. By J. K. DAWSON, D. W. INGRAM, and L. L. BIRCUMSHAW.

THE extreme reactivity of uranium hexafluoride towards organic compounds is well known (Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Vol. XII, Longmans, Green & Co.), these compounds undergoing various reactions involving the substitution of fluorine for hydrogen and the breaking of C–H bonds, whilst the uranium hexafluoride is reduced to the tetrafluoride. There is only one reference in the literature, however, to the reduction of the hexafluoride with gaseous hydrogen: Ruff and Heinzelmann (*Z. anorg. Chem.*, 1911, **72**, 82) record its immediate reduction to the tetrafluoride at room temperature. No further observations on this reaction appear to have been published, but in 1943 H. J. Spencer-Palmer (private communication) described experiments in which he treated the hexafluoride with hydrogen in various vessels at temperatures between −78° and 100° for periods of several hours; as catalysts he tried water (vapour) and technical uranium tetrafluoride; in no case was reduction observed.

From these considerations it appeared probable that the materials used by Ruff and Heinzelmann contained an impurity which acted as a catalyst, although it was difficult to see what this impurity could be since it should be presumably volatile enough to distil with the hexafluoride and also, according to Spencer-Palmer, it was not water or any of the products formed by the reactions between the hexafluoride, water, and glass. In an attempt to confirm Spencer-Palmer's work we investigated the conditions under which the reaction takes place.

The equilibrium constant of the reaction

$$UF_{6(g)} + H_2 = UF_{4(c)} + 2HF \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

may be calculated from available thermochemical data, *viz.*:

$UF_{6(g)} = U + 3F_2 - 505$ kcals.
$UF_{4(c)} = U + 2F_2 - 446$ kcals.

heat of formation of hydrogen fluoride, $\Delta H_{298} = -69{\cdot}8$ kcals.

The relevant entropy values are:

UF_6 $S^\circ_{298} = 54{\cdot}45$ cals. mole^{-1}deg.$^{-1}$.
UF_4 $S^\circ_{298} = 36{\cdot}12$ " "
HF $S^\circ_{298} = 41{\cdot}53$ " "
H_2 $S^\circ_{298} = 31{\cdot}23$ " "

Hence ΔS°_{298} for the reaction $UF_6 + H_2 = UF_4 + 2HF = 33{\cdot}5$ cals., and from the relation $\Delta G^\circ_{298} = \Delta H^\circ_{298} - T\Delta S^\circ_{298}$, $\Delta G^\circ_{298} = -79{\cdot}78$ cals. Then, by applying the well-known equation $\Delta G^\circ = -RT \ln K_p$, $K_p = 10^{59}$ at 25°; thus on theoretical grounds the equilibrium is well over to the right-hand side of equation (1) and if attained would lead to complete reaction.

A similar calculation for the reaction $UF_6 + 2H_2 = U + 4HF$ proves that in this case at 25° the equilibrium lies well to the left-hand side, but this is reversed in the region of 1000°.

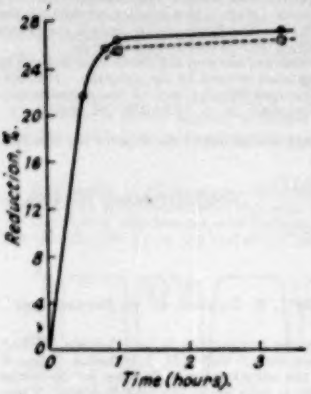
These theoretical considerations accord with Ruff and Heinzelmann's results but we have been unable to confirm them experimentally.

Experimental.—The method used was to condense, at liquid-air temperatures, a small quantity of uranium hexafluoride in a weighed Pyrex tube which was of known volume to a point marked on a constriction and was attached to a vacuum manifold. The tube was then filled with pure hydrogen (dried over phosphoric oxide), sealed at the mark, and weighed. The weight, corrected for the weight of the air originally present and also for the hydrogen present at the second weighing, gave the weight of the hexafluoride. The tubes were placed in a furnace at a known temperature for the required time and were later broken in water containing a known excess of standard potassium dichromate solution

which was then back-titrated with standard ferrous ammonium sulphate solution, tri-*o*-phenanthroline ferrous sulphate being used as indicator. The weight of the tetrafluoride formed was thus determined.

The effect of temperature was first investigated; initially the reaction time was 3 hours. The results at each temperature, although usually in close agreement, sometimes showed divergences outside the experimental limits of analysis. An excess of hydrogen was always used, the actual concentration being independent of the size of the bulb and depending only on the temperature and pressure during sealing off. In experiments at 430°, a reaction occurred in addition to the reduction of the hexafluoride, producing a purple deposit on the walls of the tube instead of the usual dark green of the tetrafluoride. In order to simplify the investigation experiments were therefore confined to temperatures below 350°, the purple compound then not being formed.

Reduction of UF_6 in a closed system. Temp. 249—250°.



The effect of temperature is shown in the table. The reaction time was 30 minutes and the initial concentration ratio, $H_2 : UF_6$, was approx. 5·0 : 1.

Temp., °	226	250	275	285	292
% Reduction	3·8	22·3	40·1	42·5	44·3
Temp., °	295	305	312	330	331
% Reduction	44·8	50·5	52·2	58·6	59·1

The effect of time is shown in the figure. The temperature was 250° and two different ratios of $H_2 : UF_6$ were used, *viz.*, 3·0 : 1 and 6·0 : 1. The results show that a large amount of the reduction takes place in the first 30 minutes. Experiments were made to investigate the kinetics of the reaction. Evidence was obtained for a homogeneous reaction in the gaseous phase, of first order with respect to each reactant, and also a heterogeneous reaction on the wall of the containing vessel. The results, however, were not conclusive and are not included.

One of us (D. W. I.) expresses his thanks for grants from the Ministry of Supply and the Department of Industrial and Scientific Research. Another (J. K. D.) thanks the Council of the University of Birmingham for the award of a Chidlaw Scholarship and the Department of Scientific and Industrial Research for a grant. The above investigation forms part of the work done on uranium compounds in the Chemistry Department of the University of Birmingham under the general supervision of Professor Sir Norman Haworth, F.R.S.—CHEMISTRY DEPARTMENT, THE UNIVERSITY, BIRMINGHAM, 15. [*Received, October 28th*, 1949.]

Some Reactions of 5-Nitroperinaphthindane-1 : 2 : 3-trione Hydrate. By RADWAN MOUBASHER and ALY SINA.

THE preparation and properties of *peri*naphthindane-1 : 2 : 3-trione * have been described by Moubasher and Awad (*J.*, 1949, 1137). We have now prepared the *5-nitro*-derivative, m. p. 215° (decomp. to a deep red melt) (Found: C, 61·0; H, 2·1; N, 5·9. $C_{16}H_9O_6N$ requires C, 61·1; H, 1·9; N, 5·5%), in the same way, and find that in its solvent properties, its reactivity towards bases [*e.g.*, aniline gives *5-nitro-2-anilino-2-hydroxyperinaphthindane-1 : 3-dione*, m. p. 267° (decomp.) (Found: C, 65·5; H, 3·7; N, 8·1. $C_{16}H_{12}O_4N_2$ requires C, 65·8; H, 3·4; N, 8·0%)], and its reaction with α-amino-acids it closely resembles the parent compound. In addition we have examined its action on ascorbic acid and dihydroxymaleic acid, and have isolated 5-nitro-2 : 3-dihydroxy 1-keto*peri*naphthindene from the reaction mixture.—FOUAD I UNIVERSITY, CAIRO, EGYPT. [*Received, August 25th*, 1949.]

* Better named as perinaphthane-1 : 2 : 3-trione. ED.

Aldehydes from Benzylamines and Isatin. By ALEXANDER SCHÖNBERG and RADWAN MOUBASHER.

SCHÖNBERG, MOUBASHER, AND MOSTAFA (*J.*, 1948, 178) suggested that the conversion of, *e.g.*, benzylamine into benzaldehyde by isatin (Traube and Engelhardt, *Ber.*, 1911, **44**, 3148) proceeds by condensation to the Schiff's base, followed by prototropic rearrangement (·CO·C:N·CH_2Ph ⟶ ·C(OH):C·N:CHPh) and hydrolysis. Angyal, Morris, Rassack, and Waterer (*J.*, 1949, 2704) showed that the reaction did not occur with 2 : 4 : 6-trimethyl- or 2 : 6-dichloro-benzylamine and objected to the mechanism just mentioned on the grounds that it should not be subject to steric hindrance. This objection is not valid, for whilst steric hindrance should not affect the prototropic rearrangement it should and does affect the formation of the Schiff's base.

We have confirmed that the starting materials are recovered unchanged after isatin (1 g.) and 2 : 6-dichlorobenzylamine (0·5 g.) have been heated under reflux in water (100 c.c.) for 1 hour.—FOUAD I UNIVERSITY, CAIRO, EGYPT. [*Received, February 23rd*, 1950.]

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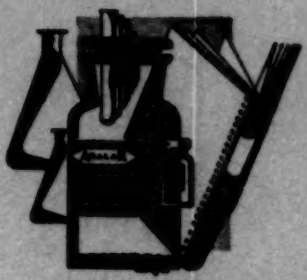

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